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RHEUMATISM AND ARTHRITIS:

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(THIRTEENTH RHEUMATISM REVIEW)*

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Part I

DEFINITION OF "RHEUMATISM" AND "RHEUMATIC DISEASES"

THESE terms apply to a heterogeneous group of conditions manifested by pain, stiffness and, in some instances, swelling and other abnormalities of joints, muscles and associated connective tissue structures. These may arise from primary pathologic processes in such tissues, from disorders of their function, or as manifestations of systemic disease. The numerous disorders included in this Review present widely different clinical manifestations, but they have a common denominator: all of them involve connective tissue. The term "connective tissue diseases" was preferred by some writers.[505] [We see little reason for the designation "collagen diseases," and consider "rheumatic diseases" most suitable until satisfactory etiologic classifications can be made.—Ed.]

GENERAL INCIDENCE OF RHEUMATIC DISEASES

To direct a search for clues regarding causation and control, and to assist in planning effective care and prevention, more and better epidemiologic information is needed on prevalence and incidence of rheumatic diseases, their temporal and geographic variation, their mildest gradients, and associated host and environmental factors. Prevalence data have been based largely upon (a) household surveys, in which

a lay interviewer asked a set of questions of either of a single respondent in the home, or of each individual being studied; (b) physicians' or institutional records; (c) clinical examination of population samples, or (d) screening procedures applied by lay interviewers to respondents at home or at work, with referral for detailed clinical, x-ray and laboratory study of those positive for screening tests. Some of these methods were more reliable than others; all had shortcomings. Even with some improvement in technics, the lay interview would not be a valid source of prevalence estimates unless accurately checked.[588, 591, 592, 1672, 1771, 3128] Problems of securing adequate response rates in population studies were explored [2627] and methods recommended for improving such rates to increase the validity of survey results.[591] It seemed probable that the epidemiologic study "would take its place beside, and share honors with, the laboratory and clinic in years to come." [592]

The actual prevalence of arthritis in general, and rheumatoid arthritis in particular, was greater than previously estimated. In Pittsburgh, the prevalence of "classical arthritis" was 71 per 1,000 persons over the age of 14; that for "classical" plus "definite arthritis" was 218 per 1,000. Most of those affected had degenerative arthritis, rheumatic heart disease with previous arthritis, or other rheumatic conditions.[591] [The criteria used in this study included all forms of arthritis. They are not those adopted for rheumatoid arthritis by the American Rheumatism Association and reported in 1959 in the Primer on Rheumatic Diseases.—Ed.] Study of a population sample aged 55–64 years in Leigh, England, revealed the following prevalence rates: all types of "chronic polyarthritis," 34.2%; "generalized osteoarthritis," 23.7%; rheumatoid arthritis, 7.1%; mixed rheumatoid and osteoarthritis, 4%; ankylosing spondylitis, 1%; gout, 1%; and psoriatic arthropathy, 0.6%.[1672] To be reliable, prevalence estimates for rheumatoid arthritis and comparability of statistics from different geographic areas required greater precision and uniformity of diagnostic criteria, and more efficient and valid survey technics. Gradients of disease severity needed to be clearly defined, since the degree to which mild or doubtful cases were included radically altered prevalence estimates.[85, 877, 1672, 1771, 2122] Largely for these reasons, available data on the incidence of rheumatoid arthritis in different countries could not be meaningfully compared.[589, 2122] Recent prevalence estimates, however, were made more comparable by adoption of clear-cut diagnostic criteria such as those recommended by the American Rheumatism Association (A.R.A.),[2588, 2589, 2590] which, despite undoubted shortcomings, could, if uniformly applied, reduce interobserver variations in diagnosis.[592] Clarification of the diagnostic significance of x-ray findings and the use of serologic tests for rheumatoid factor as an epidemiologic technic further improved the reliability and accuracy of prevalence studies,[85] though these, too, had limitations.[877, 1672] [Chiefly due to their limited ability to recognize the early case.—Ed.] In Pittsburgh the annual attack rate for "probable" or "definite" rheumatoid arthritis in those over 14 years of age was at least 5% (table 1).[589]

TABLE 1

Results of Uniformly Conducted Population Surveys of Prevalence of Rheumatoid Arthritis (RA), Defined by A.R.A. Criteria—In Pittsburgh, U.S.A., and Leigh, Lancs., England

Age	Locality	"Probable" RA	"Definite" RA	Probable or Definite RA with X-Ray Changes
15+	Pittsburgh	2.0%	0.7%	0.3%
	Leigh	3.3%	1.1%	1.4%
55–64	Pittsburgh	4.0%	0.3%	0.3%
	Leigh	12.0%	2.0%	5.0%

Rheumatic fever prevalence and new case incidence at all ages, and mortality between ages five to 15, have declined progressively in England and Wales since 1935, but trends in rheumatic heart disease incidence and mortality have not been so distinct.[1444, 2669] In tropical Africa, rheumatic fever, and particularly chorea, previously considered rare among natives, have increased since World War II.[1870]

Social and Economic Importance. In the United States, rheumatic disorders ranked second as causes of temporary or permanent disability, affected 10 million persons, caused an annual loss of 97 million work days and 500 million dollars in wages,[853, 2401] accounted for 17% of disabilities responsible for retirement of government employees between 1948 and 1955,[3108] and by their onset or progression rendered over 300,000 persons unemployable in 1953.[984] In Great Britain, "rheumatism" was a leading cause of industrial morbidity, with an annual "attack rate" of 3% in one sample of insured males;[1001] it caused a minimal annual workday loss of 9.4 million

TABLE 2

Connective Tissue Disorders Accepted as Rheumatic	Diseases and Disorders with Rheumatic Features	
I. Articular	I. Inflammatory—Idiopathic	VI. Endocrine Disorders
A. Inflammatory	(1) Dermatomyositis	(1) Acromegaly
(1) Idiopathic	(2) Polyarteritis nodosa	(2) Hyperparathyroidism
i. Rheumatic fever	(3) Diffuse arteritis	(3) Menopause
ii. Rheumatoid arthritis	(4) Scleroderma	(4) Myxedema
iii. Atypical forms of RA	(5) Systemic lupus erythematosus	(5) Osteoporosis (menopausal, senile, etc.)
(a) Psoriatic	II. Hypersensitivity States	VII. Blood Diseases
(b) Juvenile	(1) Serum and	(1) Hemophilia
(c) Felty's syndrome	(2) Drug reactions	(2) Leukemia
(d) Sjögren's syndrome	III. Traumatic	
iv. Special forms of arthritis	(1) Postural syndromes	VIII. Pulmonary Diseases
(a) Ankylosing spondylitis	(2) Traumatic arthropathy	(1) Hypertrophic pulmonary osteoarthropathy
(b) Intermittent hydrarthrosis	IV. Cutaneous or Mucosal Disorders	(2) Sarcoidosis
(c) Palindromic rheumatism	(1) Erythema multiforme	IX. Nervous System Disorders
(2) Infectional (due to specific infection)	(2) Erythema nodosum	(1) Neuroarthropathy
B. Degenerative	(3) Purpura rheumatica	(2) Reflex dystrophy
(1) Degenerative joint disease	(4) Other purpura	X. Psychiatric and Psychologic Syndromes
(2) Osteochondrosis	(5) Reiter's syndrome	XI. Neoplasms of Articular or Periarticular Tissues
(3) Intervertebral disc syndromes	V. Metabolic Disorders	XII. Osteochondrodystrophies
II. Non-Articular	(1) Alkaptonuria	
(1) Bursitis (2) Fasciitis	(2) Gout	
(3) Fibrositis (4) Myositis		
(5) Neuritis (6) Periarthritis		
(7) Tendinitis (8) Tenosynovitis		
(9) Panniculitis		

for men and 6.4 million for women.[649] In Ireland in 1950, 12,150 disability claims granted for "rheumatism" covered 228,133 weeks of work-absence, at a cost of £182,949.[2322] Rheumatic fever and its sequelae were prominent causes of rejection for World War II military service in Britain;[2973] they posed a continuing health problem among serving military personnel in the United States.[492]

Skilled epidemiologic studies of individual industries were recommended to define the pathogenetic role of occupational and environmental factors and to identify specific problems.[85, 649] Specialized rheumatic disease research and treatment units were advocated in Britain[734] and in America.[984] In a Scottish medical school, home visits supplemented bedside and outpatient teaching to provide a more comprehensive understanding of the influence of social and economic factors on arthritic patients and their families.[2503]

With the trend toward increasing life expectancy and an older population, rheumatic and other chronic disabling diseases created social, economic and health prob-

lems of mounting proportion. Coördinated efforts of the medical and allied professions, rehabilitation personnel, all levels of government, hospitals, medical schools, labor, industry, voluntary health organizations, community civic groups and the general public were essential. In the interests of national health, financial and manpower economy, there was also an urgent need for expanded facilities for research, prevention, case finding, treatment, institutional and home care, and comprehensive rehabilitation to salvage many of the disabled and restore them to wage-earning capacity, or at least to independent self-care. Substantial responsibility for amelioration of these problems rested with the medical profession, and physicians were urged to familiarize themselves with all such facilities in their communities, and to take full advantage of them.[163, 272, 360, 505, 639, 865, 886, 903, 1079, 1237, 1319, 1475, 1487, 1976, 2290, 2580, 3198, 3243, 3389]

Classification of Diseases of Joints and Related Structures

An abbreviation of the classification proposed by a committee of the American Rheumatism Association was based on a subdivision of rheumatic disorders into three major groups: I, arthritis of the various clinically definable types: II, nonarticular rheumatism in its various forms; and III, disorders in which arthritis, arthralgia or arthropathy is frequently associated.[1682] [This complete classification is contained in the Eleventh Rheumatism Review,[1k] and republished in 1959 in the Primer on Rheumatic Diseases in the *Journal of the American Medical Association.* —Ed.] The Committee on Nomenclature, La Ligue Internationale Contre le Rhumatisme, adopted the following classification in June, 1957 (table 2).[623]

The Relative Frequency of Rheumatic Diseases

The reported relative frequency of individual rheumatic syndromes varied in different hospitals and clinics throughout the world.[984, 1196, 2322] [For the reasons described above, such statistics provide no valid estimates of true prevalence of these diseases.—Ed.] The various forms of nonarticular rheumatism were the most common rheumatic entities, while degenerative joint disease was the most prevalent type of chronic arthritis.[85, 433, 1672, 2006] In tropical Africa (Nyasaland), tuberculosis, syphilis and gonococcal and other infections accounted for a large proportion of arthritis requiring hospitalization; rheumatoid arthritis was "uncommon."[1196]

Diseases Primarily Related to Trauma

Acute Traumatic Lesions. The increasing numbers of athletic events, and the greater number and higher speed of automobiles, have compelled more attention to joint injuries from accidents. The need for careful diagnosis, with full knowledge of the anatomy, and well defined structural visualization of the tissues involved, was emphasized. Recommended methods of therapy followed well established lines. The structure of the knee joint and its derangements, from simple sprain to ligamentous tears, were reviewed; special consideration was given to diagnosis.[1648, 2283] Sports injuries, including sprains, fractures and hemarthrosis, were covered.[1648, 1807, 3363] Whiplash injury, the mechanism of its production, and its numerous manifestations, including the significance of the cervical nerves and shoulder pain, were reviewed and discussed.[44, 1778, 2189] [This injury also discussed under the Sections on "Brachial Neuralgia" and "Cervical Discs." —Ed.] An attempt was made to establish a relationship between arthritis and automobile accidents, considering cause and/or effect, susceptibility to injury, and residual complications.[1778] Views on the aggravation of arthritic conditions

by trauma were expressed.[1896] In acute traumatic synovitis, with or without hemarthrosis, an interval of at least six hours usually elapsed between the injury and the appearance of swelling. This feature was reported to be helpful in differentiating this lesion from traumatic hemarthrosis in which swelling of the joint was demonstrable within one-half to one hour after injury.[1648] If the swelling was due to bleeding into the joint cavity, the joint was more tense, warmer and more painful than in simple synovitis, and might be accompanied by a systemic febrile reaction.[2283] Treatment by aspiration, compression, rest, ice bags, and early resumption of use was reiterated.[3363] Small effusions with minimal distention were treated with a snug elastic compression bandage and restriction of weight-bearing; massive effusions were aspirated and treated by the instillation of 5 cc. of 2% lidocaine hydrochloride (Xylocaine) and by hyaluronidase.[1648]

Repeated Trauma. Damage could be inflicted by dysfunction of a joint as well as by violent force. There was increasing interest in the symptoms related to, and to the dysfunction of, the temporomandibular joint. The mechanics of the "bite," of the spatial relations of the muscles, bony structures and points of contact (the teeth), and of the structural elements of the joint itself, all need to be well understood and considered in order to arrive at a clear view of this problem. The joint capsule frequently was the damaged and symptom-producing structure, suggesting that direction and strength of pull of the muscles, and of the movements of the jaw in mastication, were determining factors in production of symptoms. The complicated mechanism of the temporomandibular articulation was discussed in detail: the dual articulation within each joint, and the strict interdependence between the joints on each side of the body, the meniscus which divides the joint into two separate cavities, the condyles, the dense fibrous tissue covering the articular surfaces, the fibrous capsule of the joint, the muscles and ligaments involved in the movements of the joint—each was well described as to structure and function.[1925] These considerations were related to the types of pathology found in the joint, symptomatology and treatment. Costen's syndrome was discussed. It was pointed out that the joint is designed not to bear heavy stresses, but rather to stabilize the movements of the jaw, a role shared by the capsular ligament. Undue stresses on this ligament, of pain-producing degree, were brought about by malposition of the mandible under occlusal strain, which could result from faulty bone growth, loss or wearing down of teeth, ill-fitting dentures, or ill-advised alteration of the bite. The various classifications of joint change were described, including types of ankylosis and their implications and causes.[278, 716, 1925]

Chronic headache from dysfunction of the temporomandibular joint, a prominent feature of the symptom complex labeled Costen's syndrome,[1925] was relieved or considerably improved in 83% of 105 patients subjected to bite-correcting treatment; 11% were not improved.[239] [Costen's syndrome is also referred to in the Section, "Other Types of Arthritis and Arthritis Syndromes."—Ed.]

The differential diagnosis of temporomandibular joint pain presented unusual difficulties. Careful and complete study of all available resources, from history-taking to referral for consultation in related specialties, was needed for each patient.[470]

A study of traumatic effusions of the ankle and posterior subtalar joints was made by x-ray determinations of the size and shape of synovial pouches in 17

ankle joints injected postmortem with barium sulphate. The radiographs of 605 ankle injuries showed traumatic effusions in the ankle joint in about 40%, and into the posterior subtalar joint in 6%.

Medicolegal Aspects of Trauma. Trauma, producing or aggravating rheumatic manifestations, continued to provide issues for medicolegal litigation. A careful history, covering the time both previous to the injury and following it, was always of prime importance. Joints, when damaged, displayed the symptoms of inflammation, and the degree and duration of the symptoms depended upon amount of tissue damage, disturbance of blood supply, further damage by use or irritation, and often the initial state of the joint structures at the time of injury. Preëxisting arthritic changes might have been well established before injury called attention to them. If through the site of injury an organism gained entry to the blood or lymph, or to contiguous bone, an infection could be localized in joint tissues as a result of trauma; this controversial relationship was recognized in court.[3323]

The tug-of-war between the medical and legal professions brings about periodic attempts to find a meeting ground for agreement on personal disability litigation. Two instances are those of the Swiss National Accident Fund and the Ontario Workmen's Compensation Board. Medicolegal conclusions in the United States were said to approximate closely those of these organizations.[3323] The weight of responsibility carried by medical testimony was emphasized in a citation by the Supreme Court of the State of Washington.[3323]

Proof of disability, degree and duration of disability, capacity for work, and the prognosis were considered by Kulowski [1778] in a study of 250 patients with back injuries involving arthritis affecting the spine. In this series, about 60% required some sort of disability rating; approximately one-half were radiologically "negative." The advantages of a court-appointed expert witness and the detrimental effect of litigation were discussed. For the physical, moral and long-term financial welfare of the patients, and for the good of the employer and insurer, it was best to settle claims without litigation.[1248, 3323] Back pain was a more frequent source of litigation than was any other human ailment; but there was no such thing as "imaginary pain." [1248] The diagnosis and treatment of "traumatic" low back pain were thoroughly covered by Rose.[2596]

Treatment. Treatment of 18 patients with post-traumatic dystrophy of the extremities was reported to be more efficient when supplemented by ACTH and/or cortisone. [The diversity of conditions treated, the small number of patients, and the absence of criteria for control make it difficult to evaluate these results.—Ed.] Experiences with the intra-articular injection of a concentrated hydrocortisone preparation (150 or 200 mg. per cubic centimeter) indicated that this dosage form was superior to the conventional doses of this steroid.[634]

The use of x-ray therapy in 62 patients with post-traumatic arthritis, periarthritis and fasciitis was reported.[2990] [In this study, too, the absence of a control series renders it difficult to evaluate results.—Ed.]

Trauma was said to be the single most important factor in the etiology of coccygodynia. Of 180 patients with traumatic coccygodynia, 27 underwent coccygectomy. In the long-term follow-up of 19 of these, results were excellent in 15 and good in three; one was a failure. No criteria were found for determining which patient would be benefited by operation and which would not.[2432]

Arthritis Due to Specific Infectious Agents

Infectious arthritis was still prevalent despite the introduction of more specific therapeutic agents. The bacteriologic diagnosis was generally improved, though in some areas obscurity persisted; of 90 cases of synovitis or arthritis in Africa, 30 were of unknown etiology, and only 24 were due to identified agents.[1196] In spite of an apparent increase in the incidence of venereal diseases, interest in carrying out appropriate studies for gonorrhea[2685] was insufficient. Punch biopsy of the synovial membrane greatly facilitated direct and differential diagnosis.[2144, 2145] Mention was made of infections involving the temporomandibular joint.[470]

Gonococcal Arthritis

No reports on gonococcal arthritis appeared. Apparently the readily accessible cure and control of gonococcal infections lessened concern and thus decreased interest in carrying out appropriate studies.[2685] Continuing vigilance was required. An outbreak of gonorrhea and early syphilis involving 48 people in a "low-prevalence" area was controlled by physicians' and public health efforts; an epidemiologic analysis was made.[1004] Methods of diagnosis showed no advance; the tendency of the gonococcus to transmute into pleuropneumonia-like organisms under adverse conditions was noted.[1004, 1049] Gonorrhea as a possibly coincidental complication to the other acute forms of arthritis was mentioned; no cases were cited.[1717]

Treatment of gonorrhea with penicillin, streptomycin, novobiocin, oxytetracycline, chloramphenicol or erythromycin was described.[80, 441, 1197, 1199, 2467, 3045, 3310, 3311] One vial of 3,000,000 units of penicillin in one dose was suggested.[1199] [All in all, penicillin administered promptly after early diagnosis and in adequate dosage provided most satisfactory results, which probably explains why fewer studies appeared.—Ed.]

Tuberculous Arthritis

Even though tuberculosis was less common, tuberculosis involving skeletal structures was reported from England, Scotland, Wales, Africa (from Cairo to Cape Colony), China, Japan, Finland, Denmark, Rumania, Hungary, India, New Zealand, Canada and the United States of America. Emphasis in these reports ranged from diagnostic surveys, follow-up studies and surgical intervention to drug therapy.[52, 932, 1640, 1725] Nontuberculous limping in a child needed to be differentiated; biopsy was of value.[856] In 187 patients in follow-up studies reported from the Veterans Administration Service,[945] resistance to streptomycin was less in skeletal tuberculosis than in pulmonary tuberculosis.[969]

Incidence. In 1932 there was 156 patients, and in 1937, 170 patients with tuberculosis (about 50% of the total in each instance) in an English orthopedic hospital; in 1957 there were 25 children and 20 adults and a waiting list of five more patients with nonpulmonary tuberculosis.[935]

Clinical Data. Definitions and descriptions of disabilities and lesions from the time of Percivall Pott (1775) to the present revealed a slow-moving clinical panorama, changing with the methods of management promoted by the presenting morbidity, currently known skills, and available resources. Over the years, such innovations as the production of safe milk, mass radiography, BCG inoculations and, lately, drug therapy have altered the pattern and given hope that, with further progress, nonrespiratory tuberculosis would no longer be a problem.[935]

In New York from 1947 to 1953, primary tuberculosis was seen in 554

children 13 years of age or less; 10 had bone lesions on admission, but in a group of 171 children treated with drugs none developed bone lesions; in the untreated group of 348 patients, six of the 343 developed bone lesions after admission. Bone or joint tuberculosis occurred after admission to the hospital in five of 30 survivors among the other 35 treated patients, including those with miliary tuberculosis; the follow-up was two to eight years.[2149] A series of 142 patients with osseous tuberculosis with concurrent pulmonary lesions was reported briefly; particular attention was paid to the possibility of developing musculoskeletal tuberculosis, and to treatment of the bone lesions by surgery.

Single cases of tuberculous arthritis[514] and "tuberculous rheumatism,"[2116] in the absence of pulmonary tuberculosis were reported. A patient with tuberculous dactylitis was reported.[3388] Forty-four cases of tuberculous tenosynovitis were reviewed in a well illustrated paper.[2400] A case of multiple pseudocystic tuberculosis of bone was discovered in an aged adult.[1350] The relationship between dust, tuberculosis and arthritis among the coal miners in South Wales was discussed. Only two of 32 miners with Caplan's syndrome (simultaneous occurrence of rheumatoid arthritis and progressive massive fibrosis with a particular type of chest roentgenographic appearance) had tubercle bacilli in the sputum. Although the etiology of the Caplan lesion was obscure, the lesion contained diamino-pymelic acid, present in some gram-positive organisms, including the tubercle bacillus.[71] [Further knowledge of this syndrome may lead to its discovery and possibly lack of specificity in other localities.—Ed.]

Diagnosis. Synovial biopsy continued to be recognized as of prime value, and was mentioned in almost every article reviewed. Diagnostic problems were presented in those instances of caseous granulomas where "saprophytic" acid-fast bacilli were isolated; chronic osteomyelitis of 10 years' duration was found to be associated with these organisms.[3250] Recognition of precalculous lesions in the kidney in bone and joint tuberculosis was reported and discussed.[2217]

Bone and joint tuberculosis in children needed to be diagnosed early and to be distinguished from nontuberculous conditions.[856, 2163] Differential diagnosis among tuberculous spondylitis, juvenile osteochondrosis and congenital vertebral anomalies was presented and illustrated by 15 cases.[850]

Special Locations. A wide assortment of skeletal lesions was reported in an analysis of 230 case histories from a prestreptomycin series; most commonly affected were the major weight-bearing joints; the study included a six- to 25-year follow-up period.[1796] In this series, and in that from another source, covering 116 cases, the relationship of location of bone or joint lesions to surface, with the development of skin lesions and fistulae, was stated.[228] A case was reported of a tuberculous lesion at the site of spondylolisthesis.[2477]

Spine. That tuberculosis of the spine occurred in the United States in pre-Columbian times was established by excavations in Indian burial grounds; effigy pottery and figurines also depicted this condition.[1894] In England, spinal tuberculosis was disappearing but still remained a serious manifestation of the disease.[2541] Three cases of tuberculous spondylitis in the cervical region, presenting with nuchal rigidity and with changes in the spinal fluid, were reported.[2411] Pott's disease in 60 cases was reported, and the mechanism of psoas abscess was described.[3319] Treatment was surgical in most cases, and combined antimicrobial therapy with immobilization; the results were favorable.[3319] A study of another large series of cases of Pott's disease,[2452] involving from 2 to 13 vertebrae, disclosed the presence in five cases of double lesions with normal vertebrae intervening. Cold abscess complicated 60 of these 130 cases; paraplegia occurred in 36.[49] Spinal tuberculosis produced paraplegia in 115

patients from Capetown.[1587] One case was reported of a patient with pneumoconiosis and progressive massive fibrosis who developed spinal tuberculosis with a large paravertebral abscess.[2930] A series of 85 cases of tuberculosis of the spine was reported from India.[798] Tuberculosis of the spine occurred in 155 patients during three and a half years; general poverty, inanition (deriving in part from religious taboos), and a fatalistic attitude toward the disease were cited as contributing factors. Disturbance of the autonomic nervous system in Pott's disease of the thoracolumbar area was thought to be a factor in the coincidence of renal tuberculosis.[1481]

An excellent paper presented the differential diagnosis of tuberculous spondylitis, juvenile osteochondrosis and congenital vertebral anomalies, with illustrations from 15 cases.[850]

Hips. No new measures were reported for recognition of hip involvement. Distinction between extra- and intra-articular disease was stressed.[2971]

Knees. In 33 cases of tuberculosis of the knee, the synovialis was involved in all, and was the only site in 24; in 18, diagnosis was established from synovial tissue or fluid, and in 13 by gland biopsy; tubercle bacilli were found in one instance in curetted material, and in one in pus. Age of onset ranged from 15 months to 53 years. Bone foci were found in the tibia and femur, and in one patient in the patella.[2]

Sacro-iliac Joint. Before the days of antibiotics, tuberculosis of the sacro-iliac joint carried a mortality of 30 to 50%. Draining sinuses with secondary infection usually developed; amyloid disease with deposits in liver, spleen and kidneys occurred; cachexia and death followed. Today, the patient has a good prospect of being perfectly well.[2019]

Other Lesions. Tuberculous infection of the body and odontoid process of the axis, with a paravertebral abscess which had become retropharyngeal, and a primary latent focus in the lung, were found in a frail little lady of 72 who had had multiple abscesses in the neck many years before; presenting symptoms were dysphagia and dyspnea.[1349] Two patients with tuberculous osteitis pubis and a cold abscess in the region of the cave of Retzius were reported; osteomyelitis and osteitis pubis, the latter a bone atrophy rather than an inflammatory process, were compared.[169] Erosion of the body of the pubis was a constant feature in 11 patients, aged seven to 68, with tuberculosis of the pubis; abscess formation was present in nine, but lesions elsewhere were apparent in only four.[2274] Tuberculosis of the posterior talocalcaneal joint, with extension into talus, ankle joint, lower tibia and fibula, and os calcis,[2011] multiple pseudocystic tuberculosis of bone in an aged adult,[1350] tuberculous tenosynovitis[2400, 3353] and tuberculous dactylitis,[3388] were reported.

Treatment. Many spinal lesions were uninfluenced by treatment with drugs without operative intervention. When considerable joint destruction had occurred, surgical excision of necrotic material and arthrodesis led to healing and sound bony ankylosis. In instances of a juxta-articular bony focus with an intact joint, excision of the focus usually saved the joint; conversely, even successful bony fusion of the posterior vertebral elements did not prevent continued activity and recurrence of the infection, and paraplegia.[2542] Spinal fusion in 42 children resulted in an excellent physical status for 18 who were followed to adulthood; two boys died of meningitis.[578] Antimicrobial therapy combined with immobilization[3319] and with surgery[798] gave favorable results.

In most cases, surgical intervention was indicated, with or without chemotherapy; but with it, prompt healing by primary union was more assured. With appropriate chemotherapy, operations could be performed upon tuberculous lesions with the same degree of safety and chances for success as operations of corresponding magnitude upon nontuberculous lesions. Excision of a psoas

abscess and sequestrectomy were performed successfully in 13 patients.[3259] Analysis of 230 patients with skeletal tuberculosis who were treated during the prestreptomycin years was compared with that of a series treated with streptomycin. It was inferred that the effect of streptomycin on the osseous component of tuberculosis was slight but definite.[1796] Antibiotics and rest were successful therapy in three patients with cervical tuberculous spondylitis.[2411] If after five months of conservative therapy there was no evidence of improvement, anterolateral decompression was carried out.[1587] As a principle of therapy, the adequacy of physiologic drainage as a factor in the success of streptomycin was pointed out; lesions that were deep-seated, or surrounded by relatively avascular tissues, often failed to be favorably affected. Chemotherapy was maintained for a year or more after healing.[997] Follow-up of the initial group of cases of skeletal tuberculosis treated with streptomycin followed by early bone fusion was reported.[945] Preoperative drug therapy (average of 72 days) and chemotherapy for six months after fusion returned 17 patients to their former occupations after hospitalization of less than a year.[42] In arthrodesis, good bony contact of the surfaces to be fused was the prime requisite; positive pressure by compression maintained this contact best.[2975] General considerations were discussed, including home treatment in the absence of hospital facilities for surgery.[622, 1667] Japanese studies summarized and illustrated the advantage of focal debridement combined with antituberculous drugs.[1636, 1637, 1754] In India, rib bone from thoracoplasty was used for grafts in spinal fusion of tuberculous lesions;[796] 103 spinal fusions were reported.[797] Iproniazid, with and without surgery, in the treatment of tuberculous bone and joint lesions was reviewed.[352] Prednisolone was given in addition to streptomycin and isonicotinic acid hydrazide for bone and joint tuberculosis, but results were not significantly better; there was no contraindication to prednisolone in active skeletal tuberculosis when adequate antituberculosis therapy was being administered.[519]

The relation of chemotherapeutic treatment of skeletal tuberculosis to precalculous renal lesions was discussed.[2217] Tuberculous tenosynovitis in 44 patients[2400] was treated by careful excision of all of the involved sheaths, followed by splinting and the use of streptomycin.[3353]

The neurosurgical aspects of Pott's disease, changes in spinal circulation, and mechanical compression of the cord as pathologic factors in relation to surgery were illustrated by eight cases.[3425] One patient developed paraplegia following spinal fusion; removal of a bony ridge pressing backward upon the spinal cord failed to result in regression of the paraplegia until after an abscess appeared on the surface and followed the path of the surgical procedure. The patient then made a complete recovery.[1877] Anterolateral decompression in eight patients with Pott's paraplegia was described.[1192]

Panarthrodesis following total debridement and removal of degenerated disc and scar tissue and of sclerotic bony abscess walls, the cavity being filled with milled granules of cancellous bank bone, was described as performed in 12 cases.[1307]

Children under age 15 with tuberculous hip disease were treated, some with surgery; results in 31 patients after seven years of chemotherapy were reported.[2971] Limiting of surgery to those lesions of the hip with tissue destruction was advised.[2971]

Three patients, aged two and one-half to five, with tuberculosis of the femoral neck treated with drainage by a lateral approach, were symptom-free after 10 years; cessation of growth at the upper femoral epiphysis in one instance was noted. The added advantage of chemotherapy in conserving an intact hip joint was stated.[2478] Tuberculosis of the femoral neck in six patients under 10 years of age was treated in three cases by excision of the focus combined with chemotherapy, with excellent results. In two who were treated conservatively, recovery was slow; in the third, arthritis with joint destruction developed two and three quarter years later.[23] In 39 instances of partial synovectomy and curettage of the tuberculous hip, combined therapy made restitution of joint function possible, even after severe disease.[3308] Fixation of the hip by means of intra- and extra-articular fusion was reported and discussed; the Trumble and the Brittain arthrodeses were compared, and were illustrated by 18 cases.[1590]

Eighteen patients with tuberculosis of the greater trochanter were treated by chemotherapy and excision of bursa and diseased bone; in one patient this procedure failed, with spread of the disease to the hip joint; in two, results were good, with decreased suppuration and, later, permanent healing; and in 15 results were excellent, with healing by first intention. The value of combined therapy was illustrated by comparing its results with those in 12 patients treated by other methods—either rest in bed or sequestrectomy and curettage; in seven cases, treatment failed; results in three were good, and in two were excellent.[23] Antibiotics were used successfully in six cases of tuberculosis of the pubis; without antibiotics, sinuses persisted in one case for three years, and in two others for one year.[2274]

Synovectomy of the knee was "discarded" in adults because the two so treated lost over 80% of their flexion, but about half of the 33 patients so treated obtained full range of movement, and half of the remainder, well over 90 degrees.[2972] Five had fixed joints, the result of arthrodesis. Patients treated with intra-articular chemotherapy retained over 120 degrees of flexion, and the average period of conservative treatment was reduced by about two thirds. The difficulty of comparing present results with those of the days before chemotherapy was noted.[2972] Three patients (aged nine, 16 and 73) with tuberculous osteomyelitis of the patella were treated by radical resection or extirpation of the patella, combined with chemotherapy; following treatment, the patients were symptom-free.[2]

Tuberculosis of the sacro-iliac joint was best treated by rest and general health measures, drugs, and surgery if needed.[21] A draining sinus at the site of an earlier fusion of L-IV and L-V with the sacrum was curetted, packed, left open, and then closed after two months.[2019]

Tuberculous Rheumatism (Poncet's Disease)

The claim for recognition of this controversial diagnosis was highlighted by reports of cases. A young pilot exhibited the clinical picture of prolonged benign tuberculous involvement of lymph nodes and skin, associated with two episodes of fleeting inflammation of serous membranes, once in the knees and ankles, and once in the pleura.[2116] In three cases said to "fulfill the criteria for tuberculous rheumatism," positive Rose-Waaler tests suggested that tuberculosis and rheumatoid arthritis were coincidental.[382] [We are not certain that these "criteria" have ever been established. Much more data will be required before this entity is adequately defined.—Ed.]

Suppurative Arthritis

Infection of joints continued to demand prompt attention, recognition at the onset of symptoms, appropriate anti-infective therapy, protection, and repair if required.

Injury. A wounded joint invited infection; suppurative arthritis was said to be established when there was purulent fluid within the joint which, if allowed to remain, would lead to joint destruction.[1320] In one case, pyogenic arthritis resulted when the clenched fist was rammed against exposed teeth; the metacarpophalangeal joint was penetrated in flexion, but the punctures in skin and extensor expansion shifted with extension of the fingers and resulted in a closed contaminated space.[1660]

In Infants. Widespread prevalence of joint infection in premature infants was not apparent from reports reviewed. [This does not, however, deny the importance of the problem.—Ed.] Hip joint sepsis occurred in three premature infants who had the onset of symptoms on their eighteenth, nineteenth and sixtieth days of life; in each instance the hip was destroyed. Two other infants had the onset of symptoms in the first two weeks of life; complete recovery was reported.[1485] Suppurative arthritis of the hip was reported in a three-week-old infant.[1589] Four children between 21 months and eight years, nine months exhibited four syndromes of nonspecific spondylitis: meningeal, back pain, abdominal, and hip joint; two appeared to be staphylococcal; three yielded to penicillin; the fourth was treated without antibiotics.[835]

In Adults. A complete history and physical examination are required for an accurate diagnosis in cases in which acute joint infection is suspected. The findings may be obscure. Infectious arthritis may not be recognized until severe damage or permanent destruction has occurred because symptoms were mild or misleading.[1107] Open drainage of an infected joint, particularly of the hip, was advised.[3238] Septic arthritis developed in two patients who were receiving orally administered steroid therapy.[2162] Suppurative arthritis due to *Hemophilus influenzae* was reported in an infant[1123] and an adult.[842] Rheumatoid arthritis was complicated by severe bacterial infection of connective tissue structures in 12 cases; of these, nine involved joints and resembled exacerbations of the rheumatoid process. The infecting organisms were coliform in two patients and staphylococcic in 10, only three of whom were sensitive to penicillin.[1673] Serious infections not infrequently developed spontaneously in patients with rheumatoid arthritis.[3087] [The problem of recognizing a septic joint developing in a patient with rheumatoid arthritis receiving corticosteroids remains. Also, induced infection during intra-articular corticosteroid therapy is another cause of infection.—Ed.]

Four patients with pyoderma gangrenosum, all with fairly severe chronic arthritis, were benefited by sulfapyridine therapy.[131] In septic arthritis, roentgen findings were useful in establishing the virulence of the infection by noting the speed of destruction of joint structures.[2916] [It is preferable to have therapy under way before this develops.—Ed.] A serologic test for staphylococcal antibody was valid and sensitive in 369 patients, including those with secondary osteomyelitis, and in a large control group without staphylococcal infection. Four patients with spinal involvement presumed to be tuberculous showed a high titer, and responded to penicillin therapy by recovery and reduction of antibody titer.[1792]

Local pyogenic infection in bone adjacent to the epiphysis caused damage

which varied with the age of the bony structures. Spread of infection into joint or other structures, effect on growth, residual deformity and features of diagnosis were presented.[2800]

Bacteriology. The necessity for identification of the causative organism, determination of its sensitivity to antibiotics, and adequate administration of the effective drug was self-evident. Organisms encountered included *Staphylococcus aureus* and *Staphylococcus albus, Streptococcus hemolyticus, Pneumococcus, H. influenzae, Escherichia coli, Brucella, typhoid,* and *paratyphoid* organisms. One infant had hip joint infection with gram-negative intracellular diplococci; the mother showed a vaginal smear positive for gonorrhea.[373, 842, 1123, 1485, 1589, 1673, 2654, 2964, 3238]

Treatment. The number and type of complications were directly related to the duration of symptoms before diagnosis and treatment. Of all the complications, excluding deaths from septicemia, 85% occurred in patients whose symptoms went undiagnosed and untreated for seven or more days. Open drainage of an infected joint was the treatment of choice,[3238] but adequate antibiotic therapy, a feature of this program, improved results.[2654] To insure recovery of organisms, diagnostic aspiration preceded administration of antibiotics; a broad-spectrum antibiotic given at the time of aspiration of a septic joint could be replaced by one to which the organism was sensitive as soon as this was determined.[1589] With laboratory facilities more accessible, and with larger selection and better understanding of therapeutic agents, poor end-results became fewer, and generally depended more upon "uncontrollable factors."

Oxytetracycline provided a broad-spectrum control, and in general was well tolerated. Chloramphenicol was useful in covering a different spread of the spectrum, though its prolonged use made regular blood counts advisable.

Of 35 patients, 19 of whom were less than one year old, 26 were treated by incision and drainage and systemic antibiotics, and the other nine by aspiration and specific antibiotics only. Results were significant. Seven who were treated wthin four days of onset of symptoms by incision and drainage plus antibiotics had excellent results; pathologic dislocation of the hip was found more frequently in those treated by aspiration and antibiotics.[2654] Early diagnosis was the key to successful therapy in 51 patients of all ages with acute suppurative arthritis bacteriologically proved by joint aspiration and uncomplicated by osteomyelitis.[3238]

Brucellosis

The mild but persistent course and the difficulty of recognition make Brucellosis an important possibility to consider in patients whose diagnosis is obscure. The typical patient complained of weakness, headache, backache, insomnia, nervousness, sweats and fever; frequently, physical examination revealed no abnormalities. Spleen and lymph nodes were enlarged in about half of the patients, the liver in approximately a fifth; the enlarged organs might be tender. Most patients recovered in less than a year.[376]

Localized infection of bones, joints, endocardium, central nervous system and genitalia was produced by all three species of Brucella. The most common localization produced spondylitis; weight-bearing trauma appeared to predispose to involvement of the spine and of the joints of the lower extremities. Suppurative arthritis, with abrupt onset of painful swelling, yielded purulent joint fluid

containing Brucella, but was much less common than arthralgia. Differences between the three types of brucellosis were tabulated. Patients with melitensis infections were predisposed to a synovitis yielding sterile fluid containing lymphocytes; onset was often acute, with painful, rapid swelling without redness. Knee and ankle were most commonly involved, either as a monarthritis or a migratory arthritis, which usually disappeared after several days; there could be recurrences for weeks.[376]

Incidence. Brucellosis was reported in 342 patients in Nebraska during the years 1944 to 1955: 95 in 1947, 89 in 1948, three in 1952, three in 1953, 32 in 1954, and eight in 1955.[2962] Accidental contamination from *Brucella abortus* (strain 19) vaccine accounted for infection of a 50 year old veterinarian who inadvertently sprayed his face and eyes with this suspension of living organisms while vaccinating cattle. *Br. abortus* and its agglutinins appeared in the blood; incubation period was 31 days, rather than the generally accepted five to 21.[2640] Brucellosis in 10 children was reported from the Bath (England) clinical area; one case had been diagnosed as "tuberculous rheumatism."[3213] Spondylitis due to Brucella was reported from California, with two cases presented.

Two cases of monarticular brucellar arthritis were reported from Israel.[1977, 3177] In East Africa a disease known locally as "muhinyo" was identified as Malta fever, conveyed to man through goat's milk. In Kenya the first cases were described in 1923; the number reported rose from 25 in 1945 to 238 in 1950, with more than 100 every year since. *Brucella melitensis* was the predominant infection in the native population, but *Br. abortus* predominated in the few cases in Europeans.[857, 1990] Brucellosis in India was "not so rare," but often missed.[2032] In Indiana, 35,683 agglutination tests performed from 1946 to 1950 showed complete agglutination at a dilution of 1:40 or higher in 838; 1,998 showed incomplete reaction at 1:40. From 1,317 blood specimens, Brucella was isolated in 124 cases; all three species of the organism were represented. The diagnosis by physicians was acute brucellosis in 364 patients, chronic in 171.[910]

Etiology and Epidemiology. Control of infection in cattle reduced the incidence of brucellosis in human beings, even though the number of cattle on farms continued to increase, according to a study in Minnesota covering the period from 1927 to 1956.[1393] Brucellergin was recommended for screening tests.[3032]

Localized Bone and Joint Lesions. The most common of the localized infections in brucellosis was spondylitis. In Malta during 1947 to 1954, 6,301 cases of undulant fever were reported, and spondylitis was diagnosed in 115 of these.[3400] Of 174 cases due to *Br. melitensis* reported from Barcelona (1927 to 1955), 148 (85%) proved to have lesions of the locomotor system. There was involvement of the peripheral joints in 86 patients in this series, spondylitis in 93, and sacro-iliitis in 65, in eight of whom it was the only articular manifestation. Extravertebral brucellar osteomyelitis was very rare, and only two patients, both with costal osteitis, were reported in one series. No case was observed that evolved toward progressive chronic polyarthritis.[2614] Six cases of brucellar myelopathy with extradural cord compression were reported.[1098] One of two cases reported from Johannesburg showed a destructive brucellar lesion of the spine; the other patient had a hepatic lesion.[1518]

Diagnosis. Recovery of Brucella established the definitive diagnosis; sources of material and procedures for recovery and culture of the organism were

listed and discussed.[910, 1990, 2614, 2640, 3032, 3177] Serologic findings might be late in developing, and indicated earlier activity rather than present involvement. Skin reaction to brucellergin was a recommended diagnostic and screening test.[3032]

Radiologic appearance was characteristic only in spondylitis,[2614] but generally reflected reparative processes.[376] Bony growth, with bridge formation and ankylosis and "parrot beaks," was again described; ankylosis of the intervertebral joints was not considered to be rare in brucellosis.[3177] History of exposure[2640] and the prevalence of control of infected animals maintaining an endemic status of brucellosis were factors to suggest the diagnosis.[857, 1393, 1990, 2962, 3400] Brucellosis was "a disease of mistakes. If we do not think of it we miss it; or we may think of it and test for it, yet find nothing. It eludes us. . . ." [3213]

Treatment. The antibiotics continued as the chief reliance in the control of the infection. Chlortetracycline, 500 mg. every six hours for two to three weeks, was recommended. Streptomycin or dihydrostreptomycin, or both, were often combined with the tetracyclines. Chloramphenicol gave satisfactory results. Sulphamethazine was combined with aureomycin and streptomycin.[1990] Sulphadimidine also was used in combined therapy.[857] In the acute phase, with positive blood culture, sulfaguanidine with soluble Terramycin or dihydrostreptomycin was given in small doses for a five-day period.[2614] The relapse rate remained high, even with the newer antibiotics;[2962] 70% of patients infected with *Br. abortus* remained well after two weeks' treatment with oral chlortetracycline, 2.0 gm. daily in divided doses; 90% were permanently recovered after a second course of this treatment.[376] The effectiveness of ACTH and cortisone was discussed.[376] Surgical intervention into tissues harboring Brucella was found to be disappointing.[3177]

Typhoid Arthritis

That typhoid fever had virtually vanished in certain countries was attributed to effective protection against such early origins of epidemics as contaminated water and milk supplies. A patient with partial collapse of the eighth and ninth thoracic vertebrae and destruction of the intervertebral cartilage, and disseminated lupus erythematosus, was subjected to surgery when the spinal lesion yielded purulent fluid from which *Salmonella typhimurium* was cultured; two months after the operation the patient felt well.[2013] A Jamaican with osteomyelitis of the tibia due to paratyphoid-C recovered following surgery and chloramphenicol therapy.[3295] Reports appeared of a fatal infection due to *Sal. cholerae suis* with osteomyelitis of the third, fourth and fifth lumbar vertebrae, and a case of osteomyelitis of the acromioclavicular joint due to *Sal. typhimurium* in an elderly man who recovered.[3046] Three cases of osteomyelitis due to Salmonella in patients with sickle-cell anemia, and 33 cases from the literature, were analyzed.[1480] Children with sickle cell disease had a predisposition to osteomyelitis from Salmonella infection, with multiple bony involvement. Chloramphenicol appeared to be the most effective treatment, but was not bactericidal, and drug-sensitive organisms could persist in the tissues for months or perhaps years; erythromycin combined with chloramphenicol when sensitivity was not known was more effective.[1497]

Syphilitic Arthritis

Syphilitic arthritis was a rare condition, which might occur at any stage in congenital or acquired syphilis. General characteristics and clinical forms were described but no cases cited in a report from Chile.[1940] A male infant, nine weeks old, was the subject of a case report from India which carefully described the skeletal lesions and

included reproductions of x-ray films before and seven weeks after a 14-day course of penicillin had been given.[2224] Osseous lesions from syphilitic infection usually constituted a panosteitis; simple periosteitis did occur, but in 80% the lesion involved all elements. The classification of luetic bone lesions was reviewed and the pathology described; the outstanding roentgenographic diagnostic features of bone syphilis were reviewed: (1) multiple diffuse periosteitis; (2) osteoporosis associated with areas of sclerosis; (3) so-called lacework of bone reaction; (4) special predilection for the clavicle; (5) sclerosis of the skull.[891]

Mycotic Diseases of the Joints

Bone and joint disease due to pathogenic fungi increased in relative frequency as control of bacterial infection became more effective; increased travel, military and civilian, widened the area and assortment of exposures; more effective agents for control of several of the mycotic organisms have become available recently. Of 25 patients, eight showed osseous involvement, some with articular lesions. The cases were tabulated and described as to infective agent, structures involved, and therapy; diagnosis could be established only by recovering the organism.[3114]

Madura Foot. Twenty-one African patients with Madura foot were reported from Uganda. *Mycetoma pedis* resulted from invasion of the foot, and occasionally other parts of the body, by a filamentous fungus. It was found to be confined almost wholly to barefooted cultivators. There was swelling with little or no pain, and nodules which later formed vesicles that broke down into draining sinuses; a purulent mucoid fluid then discharged which contained the characteristic "grains," or small masses of the fungus. X-ray of the foot showed a "palisade type" of periosteal reaction, multiple sinuses and cortical erosion, the "melting snow" appearance, or a "brush-work" periosteal reaction. Osteoporosis distal to the affected bones, and absence of sequestra, were characteristic. Treatment was not discussed.[730]

Sporotrichosis. Two of 12 cases showed skeletal involvement, with bone and joint damage illustrated by x-ray in the phalanges, elbow, knee and thumb; the joints were involved by direct extension from cutaneous or subcutaneous lesions or via the blood stream, and the articular lesions were frequently multiple.[2143] A rare instance of monarticular chronic synovitis of the knee was reported in a patient who had no skin manifestations or systemic distribution of the infection.[3246] The organism was not usually found on tissue biopsy, but could be cultivated on Sabouraud's medium.[2950] Stilbamidine failed to influence the lesion, and was discontinued because of toxic effects; absolute rest and surgical excision of localized chronic granulomata followed by arthrodesis were effective.[3246] Similar results occurred in another patient.[2950]

Coccidioidomycosis. This was again described as a deep fungus infection caused by the inhalation of spores of *Coccidioides immitis;* in its primary form it was localized in the lungs and called "Valley fever," and was nonfatal. In about one in 500 Negroes and one in 1,000 whites affected, the disease became secondary, progressive and granulomatous, with a grave prognosis and a mortality above 50%. About 20% of the patients with disseminated coccidioidomycosis developed lesions in bone.[656] Involvement of the knee[1878] and polyarthritis occurring in one of two patients were reported.[2483] Chronic osseous coccidioidomycosis in 18 patients followed for from four to 29 years was described.[268] Diagnosis could be made by a skin test similar to the tuberculin test, but it was not always positive. Precipitin and complement fixation tests were reported to be positively diagnostic. A smear under high power magnification showed the typical spherical body with doubly refractile capsule, but finding it sometimes required prolonged search. The fungus could be cultured on Sabouraud's medium. In general, patients with low eosinophil count, low sedimentation rate and low fever had a lower mortality rate than did those with high levels.

Treatment was in the main ineffective, and consisted of rest, surgical excision and immobilization.[656, 1878] The lack of a satisfactory fungicide was deplored; good results from surgical excision or amputation were noted.[268] A comprehensive review of the use of amphotericin B indicated that this agent might be effective in treating coccidioidomycosis; toxic effects included evidence of renal damage, but this was said to be avoided by giving the drug on alternate days. Of four patients treated, two had knee involvement which responded favorably. The drug was too poorly absorbed from the gastrointestinal tract to achieve effective blood levels by that route; intravenous administration was deemed necessary.[1911] One patient appeared to show improvement of a lesion on the cheek after six weeks of intravenous therapy with amphotericin B; oral administration was without effect.[3320] [It would appear that this agent deserves further study.—Ed.]

Blastomycosis. It was again pointed out that this diagnosis should be considered where bony malignancy or granuloma is suspected. Although this disease was rare, the incidence of bony invasion was high. In four cases, lesions involved the trochlea of the humerus; ribs, ilium, and ischium; ilium and sacrum; and the olecranon. One had no other demonstrable lesion; three showed positive smears. Potassium iodide was used in all cases, but other measures varied with each patient. The disease was arrested for from two to almost seven years.[493]

Cryptococcosis (Torulosis, European Blastomycosis). *Cryptococcus neoformans* was again reported to be a fungus of worldwide distribution, occurring as a saprophyte on the skin and mucous membranes of men and animals; it had the unique quality of producing abundant mucoid capsular material in tissue and culture. It was considered to be more frequently pathogenic than is supposed, but invaded the skeletal system only rarely. Osseous lesions occurred in three of 21 patients, and in one of these the knee joint was involved. The roentgen findings were similar in all three patients, who showed a limited area of bone destruction with slight periosteal reaction. There were no characteristic clinical features; diagnosis could be made only by recovery of the organism.[3351] In a 10-year old Negro boy, multiple bone and joint lesions developed after injury to the left knee. Surgical drainage, curettage and a variety of medicinal agents, local and systemic, were employed, with circumstantial evidence that thymol and potassium iodide were of definite value. However, surgical removal of the diseased bone enhanced healing and lessened the possibility of dissemination.[1209]

Rarer Forms of Specific Infectious Arthritis

Yaws. Skeletal involvement in yaws was noted in 39.6% of 121 patients. Juxtaarticular nodosities occurred in yaws, syphilis, pinta, bejel and many other conditions; the difficulty of differential diagnosis was discussed. Penicillin, chlortetracycline, oxytetracycline, chloramphenicol and erythromycin were effective, but penicillin, because of its availability, low cost and ease of administration, was preferred. In late yaws, much larger doses of penicillin were required, and the type of preparation with prolonged action was preferred.[1089]

Rat-bite Fever. Since 1942, 50 cases of proved etiology have been reported in the American literature. Various features of the disease were discussed, along with one new case due to *Streptobacillus moniliformis;* this infection was compared with that due to *Spirillum minus;* arthritis was not noted in this series.[3344] Sodoku, the name given to rat-bite fever caused by *S. minus,* was reported in an English boy of 11 who had been bitten by a mouse; the organism was frequent in the nasal smear from a mouse captured at the place where the boy had been bitten.[950] Penicillin was effective against both organisms.

Osteoarticular Lesions in Smallpox. Of 12 cases in children reported from Calcutta, nine were of "subacute type" resembling pyogenic arthritis and osteomyelitis. In two cases, joints involved showed growth disturbance but a surprising range of

movement; bony ankylosis followed sinus formation and secondary infection in another. Histopathology showed bone changes similar to those seen in osteitis fibrosa.[347] Early cases improved with immobilization and supportive treatment; pure osseous lesions healed after curettage and scraping; partial excision of elbow joints gave satisfactory movement in one patient; in the other so treated, bony ankylosis followed.

Miscellaneous. Pleuropneumonia-like organisms were isolated from involved joints of two women with polyarthritis. The relationship of L-phase variants to other organisms, particularly to *S. moniliformis*, was considered.[456] The possible roles of pleomorphic forms of beta hemolytic Streptococcus or of Brucella in the pathogenesis of rheumatic disease were discussed.[419] In Australia in 1956, a mild epidemic, characterized by a maculopapular rash, usually of short duration, was accompanied not infrequently by polyarthritis. In one report, 17 cases were tabulated. In another, it was estimated that there had been between 1,000 and 2,000 cases in a community of about 20,000. Attempts to isolate a virus failed. Serologic tests were negative. It was thought likely that this and three other similar epidemics were caused by an infectious agent spread by mosquitoes from an animal reservoir.[58, 1082]

Rheumatic Fever

Occurrence. Studies concerned with incidence and prevalence were few. The initial decline in recurrence rate antedated the antimicrobial era.[3328] In Minnesota, rheumatic fever had its highest incidence in children under age 15.[1009, 1933] In San Francisco, there had been an appreciable decline in the number of active rheumatic fever cases between 1946 and 1955.[2564] However, the number of cases of recurrence of rheumatic fever remained high. In a cardiac clinic in North China, one third of all patients had rheumatic valvular disease.[1507] In Oslo, the incidence of rheumatic fever had fallen.[1735] In Bergen, Norway, data from autopsy material showed a 4% incidence of rheumatic heart disease from 1941 to 1955, without a decrease in the incidence.[3185] The average age at death from rheumatic heart disease was 52 to 53 years.[3186] A substantial decline was recorded for Wales and England.[1444, 1851] The declining trend in rheumatic heart disease was not so distinct as that for rheumatic fever.[1444] Deaths from rheumatic fever in England and Wales declined markedly from 1940 to 1953.[1851] Very few instances of acute rheumatic fever were noted in Miami, Florida, in spite of the large number of positive throat cultures for group A hemolytic streptococci.[2668]

In years gone by, rheumatic fever was not thought to be prevalent in the tropics. However, a report from India stressed that study of rheumatic fever had just begun, but concluded, without adequate epidemiologic data, that rheumatic fever ranked as a major problem of national health in India.[1787] [Previously considered rare in natives of tropical Africa, rheumatic fever, and particularly chorea, have been on the increase since World War II.—Ed.]

An inductee of the United States Army with a history of acute rheumatic fever proved to be a liability; of 302 cases of rheumatic fever among male service personnel, 29.4% gave definite or suggestive histories of previous rheumatic fever.[2603] In the British Army, a quarter of the cases gave a history of rheumatic fever.

Predisposing Factors Governing Incidence. *Season.* In a report on army garrisons in the United Kingdom, the highest incidence was in the months of March through May.[2603]

Social and Hygienic Factors. In a military setting, there was an extremely high incidence of acute rheumatic fever among recruits.[492] Statistical analysis reinforced the conclusion that a "completely unfavorable environment," i.e., low budget, inadequate clothing, overcrowding, poorly heated dwellings and an unsatisfactory diet, did influence the incidence of rheumatic fever. Overcrowding and inadequate income were significant factors in Australia.[1229]

Family, Heredity, Constitution. In Australia, "poor quality of family life," i.e., mothers who were poor managers, or who were judged to be inadequate in their relationships with their children, seemed significant in families with children with rheumatic fever, but certainly not etiologically so.[1229]

In an attempt to correct the genetic expectation for siblings who had not passed the *complete age of onset range,* a reappraisal of families with rheumatic fever revealed the increase in number of cases to be insufficient to affect the previous conclusions.[2970] There continued to be a significantly higher proportion of affected subjects among siblings of propositi with affected parents.

To avoid the statistical influence of family size, families of the *same size,* and in which there was a known case of rheumatic fever in parents, were compared.[766] Rheumatic fever occurred with greater frequency in families with positive histories. However, in Miami, Florida, the observed number of rheumatic fever patients was only one third the predicted number; this did not corroborate Wilson's thesis that rheumatic susceptibility is a single, autosomal, recessive characteristic.[2671]

Sex. In a cardiac clinic in North China, in the 12 to 20 year age group, there was no sex difference, but in the third and fourth decades females led, "probably because of obstetrical conditions."[1507] In the 50 to 80 year age groups in Oslo, women were affected more than twice as often as men.[1735] Among Negroes in a large hospital in the southern United States, the female-to-male ratio was 1.7:1.[1895] In Cardiff, Wales, signs of permanent cardiac damage were more frequent in girls than in boys.[1444]

Age. In Oslo, Norway, there was an increased incidence of rheumatic fever in those over 50.[1735] The highest incidence continued to be noted in children up to the age of 15 years.[1009]

Race. In a large hospital in the southern United States, only 12% of 162 patients were white; the rest were Negro.[1895] [Total hospital admissions were 75% Negro, making for a highly selected group. The only possible conclusion is that rheumatic fever occurs in the Negro.—Ed.]

General Clinical Data and Relative Incidence of Clinical Manifestations. Papers outlining and giving percentages on clinical manifestations were scarce. There were a number of reports concerning clinical data.[186, 509, 533, 1467, 2023] No new facts were reported.

Pathology and Clinicopathologic Data

Current knowledge of the relationship of group A beta hemolytic streptococcal infection to acute rheumatic fever was summarized.[2465] A general review of the pathology of rheumatic heart disease appeared.[1206] The distribution of rheumatic involvement of the four cardiac valves in four autopsy series paralleled the physiologic pressures sustained by the valves, i.e., mitral, aortic, tricuspid and pulmonary, in order of decreasing pressure and incidence of involvement.[3143]

Histochemical studies of rheumatic valvular lesions suggested that the hyaline material of acute and chronic valvulitis was fibrin, and that the sequence of events in evolution of valvular disease was (1) endothelial injury, (2) thrombosis, and (3) organization and vascularization.[3141] In a 20-year study of 2,000 cases of rheumatic fever, 87 cases of severe aortic insufficiency were encountered;[284] twice as many of these were in males as in females. The 20-year mortality of patients with severe aortic insufficiency was 56%. A clinical and pathologic study of 35 cases of fatal rheumatic pneumonitis emphasized the frequency of severe respiratory symptoms which were out of proportion to cardiac or general systemic manifestations of rheumatic fever.[1956] Other reports on rheumatic pneumonia concerned the nonspecificity of the clinical picture, its association with severe carditis, and its poor prognosis.[412, 1185, 1329, 1532] Although the incidence of nongranulomatous uveitis in rheumatoid arthritis was appreciable, none of 200 patients with acute rheumatic fever demonstrated this involvement.[2860] Twenty-four of 233 patients with rheumatic fever had cutaneous changes attributable to the disease.[484] These lesions included erythema multiforme, erythema nodosum, urticaria, purpura and subcutaneous nodules. The postcommissurotomy syndrome was not an expression of true rheumatic activity, but "accentuation, persistence and recurrence of normal postoperative sequelae."[2339] Severe necrotizing arteritis of the aorta and pulmonary artery in a seven year old boy with rheumatic carditis was reported.[2662] Uncommon features of rheumatic fever, i.e., involvement of the central nervous system and the lungs, diffuse vasculitis, peritonitis and glomerulonephritis, were reviewed briefly.[3104] [How many of these represent systemic lupus erythematosus or hypercortisonism?—Ed.]

Capillary microscopy of conjunctiva and nailbeds in patients with rheumatic fever or rheumatic heart disease demonstrated specific vascular features which were less frequently encountered in control patients.[733] The possible relationship of susceptibility to rheumatic fever and genetic constitution was explored by analyzing blood groups of 260 rheumatic patients. The incidences of blood groups A, B, O, M, N, S and Rh were not significantly different from those of a normal population.[3215] Patients with severe rheumatic fever demonstrated increased sodium spaces and increased exchangeable sodium, suggesting a shift of sodium into cells or bone.[27] Attempts to isolate on human fibroblasts a virus from auricular appendages obtained at mitral commissurotomy were not successful.[1786]

Laboratory Data

Electrocardiographic Studies. In 500 normal children up to the age of 13, both age and heart rate exerted a significant influence on the PR interval.[40] There was a wide range of normal PR intervals in children; the degree of change in serial electrocardiograms was more important than any given interval duration on a single tracing.[1132]

Sedimentation Rate and Alterations in Serum Proteins. The occurrence of certain abnormal substances in the blood in a variety of inflammatory conditions was referred to as an "acute phase" phenomenon;[858, 989] these "acute phase" reactions were discussed extensively,[13, 436, 869, 989, 1345, 1883, 1941] and their nonspecificity was emphasized.[989, 992] The relative merits of certain of these reactions in detecting the inflammatory reaction in rheumatic fever and in assessing the activity of the process at various stages in the disease were discussed.[13, 436, 600, 741, 844, 989, 992, 1132, 1345, 1419, 1883, 1941, 2424, 2625, 3103]

The two most widely used measures of the "acute phase" reactions and the most frequently compared were the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP).[741, 989, 992, 1345, 2625, 3103, 3204] Fischel reviewed some of the advantages and disadvantages of each, and stated that "in most instances both tests were normal and abnormal simultaneously," but that "in those instances where there is a discrepancy, it is far more common to have an abnormal ESR in the presence of a normal CRP than the reverse."[992] "The Westergren sedimentation rate remained one of the most valuable laboratory tests for the presence of inflammation"; the CRP determination was an auxiliary test which "occasionally might provide additional information, particularly in the very early stages of the inflammatory reaction." Advantages of the Westergren technic over others for sedimentation rate determination were discussed.[954, 989, 992] Serious discrepancies in parallel sedimentation rate determinations were noted when heparin was used as the anticoagulant.[37]

The nonspecificity of the CRP test was reëmphasized,[13, 436, 741, 858, 989, 992, 1011, 1743, 1744, 2625, 2729, 3103, 3131, 3386, 3402] but some workers considered the CRP test to be the most useful index of inflammation.[741, 1883, 3386] It was the view of many that it tended to appear earlier in the course of rheumatic fever than did abnormalities in other indices.[989, 992, 3386] As patients improved under therapy, it tended to revert to negative more rapidly than the sedimentation rate returned to normal.[741, 989, 992, 1345, 3386] A negative CRP test in the absence of clinical evidence of activity suggested that rheumatic activity had subsided;[741, 1345] however, it was difficult to assess rheumatic activity, and, despite a normal CRP and/or ESR, subclinical rheumatic activity could be demonstrated in some patients.[436, 992] In some instances of rheumatic fever with congestive heart failure, the CRP was positive, while an initially normal ESR rose to abnormal levels only after the hepatic congestion had been relieved.[1345] It was frequently positive in postoperative patients without complications.[2473] A flocculation technic[3131] and a quantitative complement fixation technic[2474] for CRP determinations were described. Characteristics of the C-reactive protein itself were studied,[1551, 1888, 2516, 2647] and were similar in fluids from serous cavities in patients with various diseases.[1888] It was found in the gamma-globulin range on continuous zone electrophoresis.[1551] An antigen in carbon dioxide precipitates of sera from patients with rheumatic fever and other inflammatory conditions was thought to represent C-reactive protein.[2516]

Other "acute phase" indices included plasma fibrinogen levels[1941, 2500] and a "fibrinogen polymerization" test.[1941] Elevation of serum mucoprotein levels was found to be useful as a nonspecific index of inflammation.[13, 436, 1883]

Elevated levels were also noted in diabetes mellitus and atherosclerosis.[1144] An attempt was made to demonstrate specific chromatographic patterns of the serum mucoids in a variety of diseases.[2438] The anticipated elevation in rheumatic fever might be somewhat suppressed in the presence of congestive heart failure.[1345] The diphenylamine (DPA) reaction[600] reflected serum mucoprotein levels.[1419] A simple colorimetric test for the determination of the sialic acid of mucoprotein was useful in evaluating the inflammatory response.[1419] The rise in serum hexosamine in rheumatic fever and other inflammatory conditions was shown to be associated with a selective increase in the hexosamine/protein ratio of the hexosamine associated with alpha-1 globulin.[332] Serum glutamic oxalacetic transaminase (SGOT) was slightly elevated in some—but not all—patients with carditis.[2025]

ACTH, adrenal cortical steroids and salicylates exerted no effect on positive CRP reactions in advanced neoplastic disease;[1881, 2331] similarly, sodium salicylate did not affect abnormal ESR and CRP determinations in febrile reactions following the injection of killed *Aerobacter aerogenes*.[1390] Thus, the reversion of these determinants to normal during the treatment of rheumatic fever was due to suppression of the inflammatory reaction, rather than to any direct effect of the medications on the responsible

serum protein abnormalities.[992, 1881, 2331] A reaction following the use of benzathine penicillin in some convalescent rheumatic children was characterized by fever, appearance of C-reactive protein and rise in ESR, and could be confused with recrudescence of rheumatic activity.[1287] [This effect was not noted with procaine penicillin in these children.—Ed.]

Other Studies. The antistreptolysin-O titer (ASO) as evidence for streptococcal infection (but not for rheumatic fever itself) was discussed,[21, 45, 1883, 2643] and in one report was disputed.[534] Factors influencing this determination and their significance were reviewed in detail.[1492, 2045] The ASO and streptococcal antihyaluronidase titers showed a greater fall in one month in patients treated with ACTH and cortisone than in those not so treated.[1343] Twenty rheumatic fever patients under the age of six had a lower mean ASO titer and a lower frequency of raised titers than did 87 older children with rheumatic fever.[1456] ASO and antistreptokinase (ASK) titers were compared with the initial CRP response to streptococcal infection; five of 57 patients with type 14 hemolytic streptococcal pharyngitis had a negative CRP test, and only these five later failed to show a significant rise in ASO and ASK titers; all five were under 12 years of age.[1889] A microtechnic for determination of ASO titers was described.[1530]

Serum cholesterol and total lipids tended to be lower in a group of quiescent rheumatic subjects than in their nonrheumatic siblings.[535] In acute rheumatic fever, no appreciable alteration was noted in the total lipoprotein/alpha lipoprotein ratio.[241]

Relationship to Other Diseases

The postcommissurotomy syndrome had no relationship to the rheumatic state.[1828] No correlation was found between rheumatic fever and multiple sclerosis,[2289] but many more rheumatic fever histories were found among nonparanoid schizophrenics than among paranoid schizophrenics.[3283] A history of previous rheumatic fever was noted in one quarter of a group of patients with rheumatoid spondylitis; it was thought that most instances of valvular heart disease with rheumatoid spondylitis were due to rheumatic fever.[1468] [Some of us do not agree. The constitution of the group of spondylitic patients was influenced by artificial selection, in that all patients with peripheral joint involvement were excluded. There is good evidence that there is a form of heart and aortic disease, usually with aortic insufficiency, which is apparently specific to patients with ankylosing spondylitis, and for which no sound evidence of "rheumatic" etiology has been established. This lesion has its greatest prevalence in spondylitic patients with peripheral joint involvement. It is very difficult to assess the reliability of the past history of so-called "rheumatic fever" in spondylitic patients. Not uncommonly, these individuals give a history of an atypical episode of peripheral joint polyarthritis which was mistakenly diagnosed as "rheumatic fever" at the time, but which, in retrospect, much more probably represented a peripheral joint onset of ankylosing spondylitis. Subsequently there may have been a sustained remission of the peripheral joint arthritis while the spinal involvement progressed. This is not an uncommon course for this disease to follow.—Ed.]

Differential Diagnosis

The differential diagnosis included systemic lupus, brucellosis, rheumatoid arthritis and other syndromes.[14, 955, 1107, 1286, 1298, 1309, 2112, 2372, 3212]

Course, Prognosis and Results

Steroid treatment influenced the natural course of the carditis.[3327] The major factor influencing morbidity and mortality in the third, fourth and fifth decades

was the residual damage sustained during the first and second decades of life.[1974] The survival curve for patients with mitral insufficiency followed closely that of the general population: patients with mitral stenosis and insufficiency had a lesser rate of survival.[3329] Manifestations of rheumatic fever following cessation of treatment were directly related to underlying disease activity.[991]

Etiology and Pathogenesis

Several good reviews of the etiology and pathogenesis of rheumatic fever appeared, with comprehensive bibliographies.[502, 692, 1175, 2043, 2463] The more widely accepted theories on the role of the streptococcus, the method of transmission, the role of the host, and the question of the importance of hypersensitivity to the streptococcal organism were discussed. The necessity for the persistence of viable streptococci during the period of activity of the disease,[2043, 2464] the correlation of the occurrence of acute rheumatic fever with the period of hyperinsulinism during the convalescent phase of acute streptococcal infections,[1932, 1934] the possible value of egg yolk as a preventive,[1932, 1934] the protective effect of diabetes,[1934] and a rather vigorous claim for the importance of the role of allergy [685] were the major topics discussed in the evidence reviewed for less commonly held viewpoints.

The question of whether rheumatic subjects over-respond to antigenic stimuli had not yet been resolved. In three different experimental models, rheumatic children had higher ASO responses to injected SLO than did nonrheumatic children,[2451] and children with inactive rheumatic fever tested with Brucella antigen showed increased reactivity, as measured by the level of incomplete antibody and Brucella agglutinins.[2332] On the other hand, the response to diphtheria toxoid in Shick-negative individuals with acute rheumatic fever or a history of it was the same as that of the controls in the amount of precipitating antitoxin and probably in the amount of nonprecipitating antitoxin formed.[2450] That rheumatic subjects were hypersentitive to the streptococcus suggested that the intense antigen-antibody reaction damaged endothelial cells.[2829] The ASO tended to be high in children with acute rheumatic fever and articular manifestations, and close to normal in those with carditis without arthritis; these findings suggested two different pathogenic mechanisms.[529]

Three attempts to demonstrate an auto-immune mechanism in rheumatic fever were reported, using Coon's fluorescent anti-human gamma globulin. Vazquez and Dixon showed a localization of gamma globulin in the hearts of patients with rheumatic carditis that was not found in the hearts of patients dying without heart disease, or with nonrheumatic heart disease.[3167] Some (though less) fluorescence was noted when fluorescent anti-human albumin was used. [The authors wisely refrain from drawing any conclusions from this work.—Ed.] Two Czechoslovakian workers tested for the presence of auto-antibodies to the several tissues involved in rheumatic fever by doing agglutination reactions between the serum of patients and salt extracts of normal human tissue. In a well controlled and careful study, no agglutination was found with serum of normal controls, while the serum of acute rheumatic fever patients agglutinated with many of the tissue extracts. An inverse relationship between clinical evidence of carditis and the presence of agglutination of the patient's serum with heart tissue was noted, suggesting absorption of antibody on the patient's heart in these cases.[3195] A similar study, using principally liver and kidney as antigens, demonstrated that the sera of patients with so-called "auto-immune" diseases, including acute rheumatic fever, tended to bind complement in the presence of these antigens to a greater degree than did sera from controls.[1093] There was some suggestion that fibroblasts and leu-

kocytes of patients with acute rheumatic fever were more sensitive to the products of the streptococcus, as measured by inhibition of growth, depression of migratory ability and transformation of the white blood cells to spindle-shaped forms.[1012, 1013, 3265]

A report demonstrating that a rheumatic population had a small but significantly greater percentage of Le(a +) secretors [blood-group types.—Ed.] than did a control population suggested that there was a genetic factor in this disease, and that the Le(a +) antigen might be haptenic in the pharynx, but became antigenic to the host when absorbed on the streptococcus.[1163] The urinary glucuronides tended to decrease in the active stage of various "rheumatic diseases," including acute rheumatic fever, when compared with normal controls. [No controls were done with patients with other inflammatory diseases.—Ed.][1472]

The presumed rheumatogenic effect of the β-streptococcus was demonstrated by production of a myocarditis in rabbits after induced streptococcal pharyngitis without arthritis or a rise in an associated ASO or erythrocyte sedimentation rate.[1151] Group A streptococci grown in beef heart cause transient rises of complement-fixing antibody to normal rabbit heart when injected intradermally.[1630]

Streptococci from patients with acute rheumatic fever were culturally, enzymatically and serologically identical to those from other infected patients or carriers.[1331] The lower incidence of rheumatic fever in Florida than in northern areas of the United States could not be explained by differences in the type of organism found.[2670]

Treatment

Rest. The importance of bed-rest in the acute stage of the disease, with a graded return to physical activity as soon as consistent with control of signs and symptoms, was again emphasized.[173, 466, 2471, 2741, 2991] The possibility of early ambulation (within 48 hours) and the importance of avoiding prolonged unnecessary bed-rest were stressed.[1133] In convalescents, the eventual degree of activity varied with the severity of cardiac involvement: unlimited activity for those without carditis or chorea, ordinary activity without competitive effort for those who had carditis only, a gradual increase to maximal capacity for those with heart disease and carditis.[1443, 1848, 3358] Help from psychiatrist and psychiatric social worker was valuable in overcoming the emotional problems of young patients faced with inactivity and convalescence.[84, 1010, 1238]

Salicylates. The principles of salicylate therapy discussed in previous reviews were reiterated.[466, 1125, 2020, 2024, 2471, 2741, 2991] Salicylates still seem to be the drugs of choice for the majority of patients. Disappearance of glycosuria and return of fasting blood sugar to normal in a young diabetic during aspirin treatment for acute rheumatic fever led to reinvestigation of the effect of salicylate in diabetes mellitus.[2499] Although a rare complication of salicylate therapy, encephalopathy was reported in a patient with acute rheumatic fever and a blood salicylate level of 50 mg.%.[1476] Plasma salicylate levels were not an absolute guide to imminence of toxic reactions; marked hyperpnea was to be considered a warning sign.

A preliminary report was made on the effectiveness of a number of compounds with a modified chemical structure of salicylic acid.[572, 573, 574] Some—among them gentisic acid, gamma resorcylic acid and phloroglucinol acid—proved to have a greater antirheumatic effect by weight than did salicylic acid, and in the few patients tested had no toxic effects. The tri-phenols, especially 2, 3, 6-trihydroxy benzoic acid, were found to have the highest antirheumatic potency, as well as to be nontoxic. Salicylamide was rapidly absorbed and excreted; it was difficult

to obtain and maintain high blood levels. Doses of 6 to 12 gm. daily had an analgesic effect in rheumatic fever. Since it was not converted to salicylate, it could be given to patients allergic to aspirin. Although tolerated better than aspirin, high doses could cause gastrointestinal distress and dizziness. Acetophenetidin (phenacetin), acetanilid and N-acetyl-p-aminophenol were reported to have had the same analgesic effect as salicylate.[1070]

Twenty-five compounds representing structural derivatives of benzoic acid were tested for raising the circulating 17-hydroxycorticosteroids in guinea pigs through doses equivalent to 200 mg. of salicylic acid per kilo of body weight.[799] While aspirin exerted the greatest effect on plasma 17-hydroxycorticosteroid concentration, there were many discrepancies between adrenal ascorbic acid-depleting ability and either the antirheumatic effects (when these were known) or the influence on plasma 17-hydroxycorticosteroids of these drugs.

Steroids. The use of adrenocortical hormones and corticotropin in the treatment of rheumatic fever has been well covered in the Tenth, Eleventh and Twelfth Rheumatism Reviews.[1j] Divergent opinions on their effectiveness in preventing cardiac damage continued to be expressed. [The editorial comment in the Twelfth Review,[1l] that "the final answer will not be known for many years and the difficulties in early diagnosis will make interpretation difficult even then," can also summarize the situation up to the present.—Ed.] Two editorials presented the current confusion of the practitioner.[585, 852] An excellent review of the literature up to 1956 was published.[986]

Steroids were advocated to prevent or minimize cardiac damage.[551, 1129, 1134, 1385, 1443, 1665, 1666, 1937, 2022, 2024, 2055, 2741] Significant murmurs disappeared with greater frequency in those patients receiving large doses of cortisone or corticotropin for long periods than in those receiving small doses. In both groups, the shorter the duration of illness prior to therapy, the greater the frequency of disappearance of murmurs.[2623] This and similar studies on the effect of dosage of steroids were criticized on the basis of small numbers of patients, relatively short follow-up, inclusion of mild cases in the groups treated early, and the impossibility of making in all cases an absolute diagnosis of rheumatic fever within two weeks.[194]

A carefully controlled study was reported of a group of 100 patients divided into three groups—no carditis, initial episode of carditis, and recurrent carditis—receiving three treatment schedules, corticotropin, cortisone and symptomatic (with minimal salicylates). Observations on such patients during the period of hospitalization did not indicate any significant difference between hormone-treated and control subjects in terms of appearance or disappearance of cardiac murmurs, degree of transmission of apical systolic murmurs, incidence and duration of pericarditis, or other cardiologic phenomena.[1346] [Reservations regarding these conclusions must be made, however, because of the number of patients involved and the limited observation period.—Ed.]

Practically all seemed to agree, however, that steroids should be used in severe cases where salicylates failed to bring under control an apparently fulminating and potentially fatal form of the disease.[173, 194, 1346] Clinical uses and hazards of adrenal steroids in the rheumatic diseases were described, and some comment pertinent to rheumatic fever was made.[335, 434, 1402, 2416]

Although the relatively short term of adrenocortical therapy used in rheumatic fever does not carry the same dangers as do those of long-term treatment of rheu-

matoid arthritis, adverse side-effects were reported. A psychotic episode appeared in an adolescent girl with an unstable environment.[15, 1193] Prednisone in amounts of 100 mg. daily for from 40 to 171 days was used to prevent cardiac sequelae, but had to be discontinued because of the development of osteoporosis and compression fractures in three of 11 children with acute rheumatic fever.[2868] During the early post-treatment period, five children developed pruritus and erythema nodosum-like lesions; in two, panniculitis with perivasculitis occurred. In two children, congestive heart failure developed 25 and 60 days after cessation of hormone therapy without clinical evidence of rheumatic fever. At the autopsy of one who died, no evidence of recrudescent rheumatic fever was found but multiple vascular lesions were prominent.[2868] [Was this the vasculitis of hypercortisonism?—Ed.] A patient with cardiac involvement who became worse on 60 mg. of prednisone daily responded within 24 hours to 300 of cortisone. Cortisone over a period of one year had a favorable effect on the subcutaneous nodules of a patient diagnosed as having rheumatic fever.[60] [Probably rheumatoid arthritis with a natural remission.—Ed.]

In the Co-operative Clinical Trial in 1955, most patients exhibited reappearance of some manifestation of rheumatic activity in the three weeks following cessation of steroid therapy for acute rheumatic fever.[988] While these in general consisted only of elevation of sedimentation rate and temperature, severe and complex manifestations could occur. A combined salicylate and corticoid therapy was advocated to overcome this rebound phenomenon.[990] [Much of the early difficulty with steroid therapy in acute rheumatic fever can be attributed to difficulties in diagnosis and attempts to treat patients with arbitrary dose schedules. Steroids are still a valuable therapy for this disease.—Ed.]

Laboratory Changes Associated with Hormonal Administration. Children with initial or recurrent attacks of rheumatic carditis showed normal levels of urinary neutral 17-ketosteroids, serum corticoids and serum protein-bound iodine prior to cortisone or corticotropin therapy. With hormone therapy, the protein-bound iodine decreased slightly, with no evidence of thyroid hypofunction. Serum corticoids and urinary 17-ketosteroids were increased. Neither the presence nor the intensity of those laboratory changes showed any relationship to the clinical outcome.[1241] Prolonged therapy with cortisone or corticotropin in rheumatic fever was characterized by a relative decrease in the potassium as well as the sodium content of the body;[26] these findings indicated that the change was due to an increase in the total body fat. The erythrocyte sedimentation rate returned to normal more slowly in overweight children receiving cortisone than in underweight children receiving comparable doses of the hormone;[1513] this difference was not noted in those receiving salicylates alone. The results were unexpected, and the reason for them was not clear. The circulating eosinophil response during steroid therapy reflected the adequacy of steroid dosage, and presaged a rebound of activity of the disease.[1898]

Chemoprophylaxis. Adequate doses of penicillin to eliminate completely the hemolytic streptococci in patients with active rheumatic fever were generally recommended.[194, 377, 551, 1443, 1666, 2022, 2024, 2173, 2741, 2991] Single intramuscular injections of 600,000 to 1,200,000 units of benzathine penicillin, 600,000 units of procaine penicillin G in 2% aluminum monostearate intramuscularly every third day for three or four doses, or 300,000 to 600,000 units of aqueous procaine penicillin G for 10 days might be administered as alternative therapy. [Massive penicillin therapy for acute rheumatic fever remains controversial.—Ed.] It was again stressed that sulfonamides should not be used to eradicate hemolytic streptococci.[1446] That medicine is an art was shown by a report of the effectiveness of

percutaneous injections of fresh ox bile as a therapeutic agent in rheumatic fever and other diseases.[2237] [This has not been proved.—Ed.]

Prevention of Rheumatic Fever

Control of Acute Streptococcal Infections. No major changes in the recommended therapy of acute streptococcal pharyngitis or the carrier state were made. The difficulty of clinical diagnosis was emphasized.[2799] Penicillin remained the drug of choice, and treatment schedules were outlined.[2992, 3366] The duration of therapy was of more importance than was dosage; maintenance of adequate blood levels for a 10-day period was necessary for eradication of the organism. An increased incidence of acute rheumatic fever was noted in incompletely treated patients; rheumatic attacks developed in 76 of 5,198 infections and persistent group A streptococci could be cultured from 82% of these cases.[518] Oral phenoxymethyl penicillin (penicillin V), in a dosage of 200,000 units three times a day for 10 days, was effective in achieving a 90% clinical remission and bacteriologic cure in 110 cases of streptococcal infection in children.[3256] Although the stability of this preparation in an acid medium resulted in more dependable absorption, it was not recommended to replace parenteral forms of the drug.[441] A comparative study of various oral penicillin preparations and intramuscular benzathine penicillin G in the treatment of acute streptococcal infections revealed that the latter was superior, but that painful local reactions might prevent its use.[379] Benzathine penicillin G (Bicillin) was effective in mass prophylaxis of epidemic infections,[2063] or in the treatment of the carrier state. Five hundred ninety-seven of 624 recruits became culture-negative for at least one month after a single injection of 600,000 units of benzathine penicillin G.[402] No cases of acute streptococcal infection were seen for 44 days in a series of 246 recruits who received 1,200,000 units of benzathine penicillin G during an epidemic of streptococcal infections.[2199] However, in civilians, prophylactic sulfonamide or penicillin did not prevent secondary infections in the siblings of patients already infected.[378] Significant resistance to penicillin of group A hemolytic streptococci has not developed.[2470] The inefficacy of sulfadiazine in the therapy of acute streptococcal pharyngitis was again demonstrated. Eighty-eight per cent of 261 patients treated with 4 gm. of sulfadiazine a day for five days continued to exhibit the organism on throat culture, and 5.4% developed acute rheumatic fever, which occurred in only 4.2% of untreated control subjects.[2200]

Prophylaxis for Prevention of Recurrence of Rheumatic Fever. Chemoprophylaxis for prevention of recurrent attacks of rheumatic fever was universally accepted.[2044, 2992, 3359, 3366] The pattern of streptococcal infection and the results of various prophylactic programs were analyzed.[2158, 2159] Comparison of the attack rates of streptococcal infection per patient year in 405 rheumatic children followed over a two-year period showed that those receiving 1 gm. of sulfadiazine per day had a rate of 0.24; those receiving oral penicillin, 200,000 units per day, had a rate of 0.20; those receiving benzathine penicillin G, 1,200,000 units intramuscularly per month, achieved a rate of only 0.07 streptococcal infections per patient year.[3357] In 118 rheumatic children followed for a period of from six to 32 months on a regimen of benzathine penicillin G, 1,200,000 units intramuscularly every 28 days, only 13 of 2,817 nose and throat cultures contained group

A hemolytic streptococci. Four patients showed significant rises in antistreptolysin O titer, but no cases of recurrent rheumatic fever developed.[769] The incidence of reactions to intramuscular benzathine penicillin G was low, but an anaphylactic death was described in another series.[1491] Approximately 3% of 3,275 patients receiving penicillin, either 600,000 units every four weeks or 900,000 units every six weeks, exhibited some allergic response, but there were no fatal or anaphylactoid reactions. The cumulative probability of allergic response after repeated injections approached 6%.[2785] Oral penicillin G in doses of 200,000 to 300,000 units a day was also effective in prophylaxis, but had the disadvantage of allowing lapses in continuous therapy.[813, 1631, 1993] Erythromycin was of no prophylactic value in small series.[1067] Suggested drug dosage schedules of the World Health Organization's Expert Committee on Rheumatic Diseases were (1) sulfadiazine, 1.0 gm. per day; (2) benzylpenicillin (pencillin G), 200,000 units twice a day; (3) phenoxymethyl penicillin (penicillin V), 100,000 units twice a day; or (4) benzathine penicillin, 1,200,000 units intramuscularly once a month, or 600,000 units twice a month.[3366] There was no unanimous opinion on the optimal duration for prophylaxis. Some investigators felt that the difficulty in diagnosis of an acute streptococcal infection and the relatively high recurrence rate of acute rheumatic fever in adults despite long latent periods from previous attacks indicated continuous and lifelong therapy.[2205, 2462] Factors such as age and frequency of contacts modified this viewpoint in individual cases.[2462] The possibility was entertained that prophylaxis, though modifying the appearance of acute rheumatic fever, might not prevent the development of chronic valvular heart disease.[2205, 2992] [As yet, there is no definitive evidence on this point.—Ed.]

Community Responsibility and Public Health Service. The lack of parallel between theory and practice, as demonstrated by abandonment of long-term medical observation and prophylactic therapy, was deplored.[1856, 3205] Apathy and ignorance were frequently manifest in patient, parent and physician.[462] The solution of this problem lay in the provision of community facilities for education, adequate and rapid diagnosis, and free care for the indigent. Successful rural programs[206, 1270, 2390] and a proposed urban plan[2859] were described. A system of medical registry was important.[2859, 3430] [Such a registry could provide the most valid basis for incidence, control and therapeutic observations.—Ed.]

Sydenham's Chorea

A general review of Sydenham's chorea was based on observations of 175 patients.[1864] The relationship of Sydenham's chorea to infections with group A streptococci was examined with serologic technics.[879, 3064] Seventy-three per cent of patients studied within one month of the onset of chorea had elevated streptococcal antibodies. The interval between streptococcal infection and the onset of chorea was longer than the interval for the more common manifestations of rheumatic fever. The mean duration of chorea in 170 patients was 19 weeks (range, one to 117 weeks).[1865] Acute-phase reactants and antistreptococcal antibodies were studied in 43 children with chorea (both "pure chorea" and that associated with a rheumatic history). Abnormal values were associated predominantly with the rheumatic group.[1344] A pathologic study was reported of a patient dying with chorea without other rheumatic manifestations.[617] If chorea appeared

with an initial attack of rheumatic fever, it was frequently associated with subsequent rheumatic fever recurrences.[1445] In the central nervous system, only diffuse degenerative changes were noted. Three cases of chorea in natives of East Africa were reported.[1370]

Successful treatment of chorea with chlorpromazine [904, 3341] [this has not been the experience of one of us (E.F.R.)—Ed.] and with ACTH was described. Other reports concerned the efficacy of rauwolfia alkaloids in the management of chorea.[2030, 3018] A psychiatric study of eight children with Sydenham's chorea suggested the possible role of emotional disturbances in modifying the expression of the disease.[538]

Rheumatoid Arthritis (R.A.)

Clinicians and investigators in diverse disciplines accorded unprecedented interest to this disease: the challenge of a major unknown, deliberate policies for public health, interdisciplinary collaboration, and fortuitous strides of methodology all furthered the current quest for insight into this apparently complex syndrome.

Incidence

New information came from application of standardized criteria to comprehensive population samples. The complete populations of two distinct locales in South Wales were surveyed.[2122] After a household inventory of individuals with rheumatic symptoms, and a separate screening of about 90% of the combined populations incidental to a chest disease survey, those who were considered possible rheumatoid patients were asked to report for examination. The response rate was over 90% of suspects in a total of about 25,000 persons over 14 years of age. "Rheumatoid arthritis" as defined by three sets of criteria variably included history, clinical impression, radiologic evidence in the hands and feet, and positive sheep cell agglutination test. "Obvious R.A." (positive history confirmed by laboratory or x-ray findings) was present in 4.9% of either males or females in an industrial community, and in 10.7% of females and 8.8% of males in a rural area, although on first screening females had predominated in accord with the usually observed sex ratio. [The results do not permit generalizations and definitive conclusions concerning the prevalence of R.A., but the measurement of hitherto unknown differences in manifestations probably related to R.A. refines the characterization and guides further study of the incidence of this syndrome.—Ed.] In individuals between the ages of 55 and 64 from Leigh, England, clinical, radiologic and serologic evidence of R.A. yielded prevalence rates ranging from 1% for men and 3% for women with well marked disease, to 11% and 27%, respectively, with less stringently defined disease.[1672] In a rural district of Cornwall, England, comprising 43,000 persons, the diagnosis of R.A. was established in 150 persons in some 250 homes of rheumatic suspects.[1333] The prevalence rate was calculated at 4.1 per 1000. In Pittsburgh an epidemiologic survey led to the estimate that the prevalence for "probable" plus "definite" R.A. was approximately 2.7% of the total population over 14 years of age. Another 11% of the same group met the criteria for "possible" R.A.[589, 594] [Definitive data on the incidence and prevalence of R.A. are lacking, mainly because the disease cannot be unequivocally defined. However, recent epidemiologic results are valid, and suggest that R.A. is a much more prevalent disease than was realized heretofore. Some form of registration of rheumatoid paients would provide these data. See Section on Incidence of Rheumatic Diseases.—Ed.]

Clinical Manifestations

Age and Sex. It is generally agreed that R.A. may occur at any age, though it is uncommon in childhood, and that the incidence in females rises with advancing years to a peak in the fifth or sixth decade of life. Interestingly, similar figures were reported from India, where the average age of male patients at the time of the first examination was 27.9, and of female patients, 32.9 years.[2808] In Finland, the mean age at onset was 28.6 years for men and 33.4 years for women, apparently earlier than observed elsewhere.[2743, 2744] However, in 20.6% of 471 patients, the onset of R.A. was after the age of 60.[2365] The clinical course in 50 consecutive patients over age 60 was not unlike that in younger persons; the incidence of shoulder involvement was higher, and the roentgenograms showed more osteoporosis.[805] Epidemiologic surveys confirmed the distribution of men and women among patients by ratios of 1:3 or less.[589, 1333, 1672] However, by one set of diagnostic standards used in two areas, this ratio was much higher, or equal to one.[2122] [The discrepancy may be due to choice of diagnostic criteria. On the other hand, the sex incidence of R.A. among the general population should not be assumed to be identical to that among patients at hospitals or clinics. The seeming predilection of R.A. for women is not explainable on genetic grounds. Earlier onset, as reported from Finland, could account for it, but was not a factor in the series studied at Massachusetts General Hospital, in which 70% of the patients were women, excluding patients with spondylitis.—Ed.]

Precipitating Factors. Because of the variably paced evolution of R.A., pertinent data were scarce. Evidence gathered mainly from retrospective but controlled material suggested a temporally significant relationship between the onset of R.A. and some noxious or physiologic factors which were empirically noted to precede or coincide with the disease.

Infection preceded the onset of juvenile R.A. in 19% of patients.[886] In a series of adult patients from Cornwall, psychologic stress (25%) and menopause (one third of the women) preceded the onset of R.A. by not more than two years.[1333]

Prodromal Symptoms. Constitutional symptoms associated with R.A. might precede articular involvement by weeks, months or years. Most common of these were fatigue (in some patients a sense of utter depletion), diffuse pain, loss of appetite, and vasomotor symptoms, and they occurred in the majority of all rheumatoid patients. A syndrome designated "anarthritic rheumatoid disease" bore a remarkable resemblance to the prodromal symptoms of rheumatoid arthritis.[138] [This report, by L. Bagratuni of Oxford, adds 21 cases of this syndrome to the seven cases he originally reported in 1953. It is hoped that subsequent follow-up reports of the clinical course of these cases will clarify this entity.—Ed.]

Onset. The earliest localized signs of R.A. in some patients were tenosynovitis,[1548] uveitis[3362] or Morton's metatarsalgia.[3154] Morning stiffness occurred with such regularity that it was *sine qua non* in rheumatoid arthritis.[3091]

Articular Manifestations. The destructive effect of R.A. on articular tissues varied with individual patients and joints; it was slight in some joints with long-standing effusions, but marked in others affected for only a few weeks. Deformities in the hands of 300 patients with rheumatoid disease[387] and the types of "contractures" in 305 R.A. patients[1799] were recorded. [It is surprising that there are few detailed accounts of these deformities in the literature. With recent advances in surgical reconstruction of the crippled arthritic, these two well illustrated

papers are of considerable and timely interest.—Ed.] Attention was again called to bony ankylosis of the finger joints as a characteristic result of R.A. Severe and generally destructive arthritis was again reported,[1026] as was "striking involvement" of temporomandibular joints,[278, 636, 1925] and of the cricoarytenoid articulations,[144, 646, 2369] the apparent cause of dysphagia, hoarseness or stridor, severe enough in four patients to require tracheotomy.[724] Significant manifestations were dislocation of the atlanto-axial joint,[3281] and subluxations of cervical vertebrae causing pressure on the spinal cord in four patients with death in one instance.[2997] Though the cervical spine was frequently involved in adults with peripheral R.A., radiologic signs of cervical arthritis were not dependable sole evidences for the presence of R.A.[2763] A major contribution toward clarification of the nature of radiologic changes in the cervical spine in R.A. was made.[2763] A serial group of 100 patients with involvement of one or both hip joints included five instances of protrusion of the acetabulum.[2061] Phonographic recordings of crepitation were made.[1502] The propensity of rheumatoid patients to develop infectious complications was apparent in 12 patients with secondary pyogenic arthritis and infections in other areas by a variety of pathogens.[1673]

Extra-articular Manifestations. Seven adults among more than 500 rheumatoid patients had a characteristic nonpruritic, salmon-pink skin rash, usually associated with marked systemic manifestations. Macular eruptions with slightly irregular margins were about 3 mm. in diameter; occasional larger macules showed central pallor. Rarely, the rash was confluent; at times it was slightly raised. It occurred most often on the limbs and over the trunk, less often on the face and neck. It was fleeting, tending to recur with the evening rise in temperature. Duration varied from one week to 11 years, and the rash generally subsided with other evidences of rheumatoid activity.[1520] Erythema of the palms occurred in 61% and spider angiomata in 7.7% of rheumatoid patients.[285] ["Liver palms" are practically as characteristic of R.A. as they are of liver disease.—Ed.] Abnormality of the skin was suggested by prolonged fixation of Congo red dye injected intracutaneously.[1729, 1798, 2754] Some rheumatoid patients had vesicular and herpetiform lesions resembling those of pyoderma gangrenosum.[131]

Subcutaneous nodules occurred in 12% of 293 hospitalized rheumatoid patients, but were not found in unilateral R.A. or in ankylosing spondylitis. Among 305 rheumatoid patients, the incidence of nodules in flexor tendons of the fingers was 15%, and the incidence of "trigger fingers" was 5%. The latter finding, usually in the second and third fingers, was much more common in females than in males, and was associated with severer and more active disease.[2645] Tenosynovitis caused compression of the median nerve in the carpal tunnel, recognized by a positive wrist flexion test and distal sensory changes [or other signs or symptoms—see Section, Non-articular Rheumatism.—Ed.].[452, 2389] Tendinitis was frequently followed by rupture of tendons.[2429, 2914, 3005, 3262] In juvenile R.A. there was a marked tendency to flexion contractures of tendons.[884, 886] Pain on the under aspect of the heel, at one time believed to be diagnostic of gonococcal infection, was a clinical feature of rheumatoid arthritis.[452] [It may also accompany rheumatoid spondylitis, Reiter's syndrome and psoriatic arthropathy. —Ed.]

Peripheral neuropathy was observed in some patients who had never received steroids, and in others who experienced the complication within one month after

discontinuation of steroid therapy. Sensory changes predominated and preceded disturbances in motor function.[724, 1355, 1519, 2009] The primary diagnosis in 10% of 70 women with Raynaud's disease[1136] was R.A.

The occurrence of arteritis in R.A. was affirmed.[461, 545, 724, 2009] [In view of the increased number of reports of polyvasculitis with gangrene of the extremities associated with hypercortisonism in rheumatoid arthritis, the report of Bywaters[461] is of considerable interest. Only three of these 10 patients with vessel obliteration had received cortisone.—Ed.] Leg ulcers were observed in patients with R.A. who had not received adrenocortical therapy.[47, 248, 1226]

Carditis or pericarditis was reported in patients with R.A.[568, 1466, 2015, 3077, 3156] A clinical diagnosis of rheumatoid heart disease and aortic valvulitis (the seventh case then reported) was made in a 33 year old male patient who had a childhood history of rheumatic fever and chorea, developed peripheral R.A. at the age of 21, had subsequent involvement of the sacro-iliac joints, and died of cardiac failure.[2015] The term "rheumatoid aortitis" was applied to 22 male patients who, with two exceptions, had some degree of rheumatoid spondylitis.[568] Seven additional cases were recorded.[1466] The clinical differentiation from rheumatic heart disease was only presumptive, and was based principally on the concurrent R.A., usually with spinal involvement, and the absence of antecedent rheumatic attacks. It occurred almost exclusively in men, and was frequently associated with uveitis. [The opinion that these lesions are "rheumatic" is even more "presumptive." There is little or no evidence of rheumatic etiology in these cases. The most important differentiation from rheumatic aortitis and valvulitis is based on the pathologic features, which are quite distinctive. One of us (D.C.G.) found this form of aortitis to be specific for ankylosing spondylitis, and not to occur in R.A. without spinal involvement in 28 cases of carditis and aortitis studied.[1218] The term "rheumatoid aortitis" therefore appears to be a misnomer, and provides another example of the confusion caused by the policy of lumping all cases of R.A. and ankylosing spondylitis into a single diagnostic category.—Ed.]

A young woman with R.A. and acrocyanosis developed pulmonary hypertension.[1102] R.A. was associated with various nonspecific pulmonary lesions,[2009, 2874] and in Caplan's syndrome with massive pulmonary fibrosis and nodular opacities.[1628] [Apparently this was the first case reported in the American literature.—Ed.] Caplan's syndrome was not confined to miners, but was also seen seen in foundry workers and others exposed to a variety of dust hazards.[481, 487, 2533] [The relationship of Caplan's syndrome to pneumoconiosis is not yet clear. The pulmonary changes may precede or follow the onset of arthritis, and include, apart from fibrosis and round opacities, some lesions roentgenologically indistinguishable from tuberculosis. Tubercle bacilli have not been demonstrated. Rheumatoid factor is present in the serum of patients with Caplan's syndrome and in their nonrheumatic relatives.—Ed.] Pleurisy with effusion in the course of R.A. was described in six patients.[909]

The most common ocular manifestation of R.A., occurring in 14.3% of 210 patients, was keratoconjunctivitis sicca, with corneal ulceration ensuing in three patients.[3086] The incidence of all ocular lesions in 465 patients was 6.2%, and that of nongranulomatous uveitis was 3.7%.[2860] Among 209 patients with uveitis the incidence of concomitant R.A. was 10.5%.[2931] A case of bilateral sclero-malacia perforans associated with rheumatic disease and nephritis was reported.[310] The histologic appearance of these scleral lesions in two sisters with R.A. was identical with that of the rheumatoid nodule.[1994]

Special Clinical Features. Amyloidosis, a fairly common complication of R.A., was said to be rare during the early stages (up to two years' duration).[2166] A 69 year old rheumatoid woman had a cystic mass of the right breast due to extension of a periarticular bursa of the right shoulder joint and containing calcified fibrocartilage, blood clots and sterile fluid.[540] Rupture of the spleen occurred in a patient with Felty's syndrome.[1227] [This variant of R.A. does not warrant an eponym.—Ed.] In Sjögren's syndrome, auto-antibodies to salivary gland tissue were formed.[1586] Sialography revealed the degree of atrophy, and the extent of the sclerotic process and the undamaged parenchyma of the salivary gland.[3093] Sjögren's syndrome was said to have a poor prognosis.[3036] [The presence of the "sicca" syndrome does not render the prognosis any worse than that of the severe systemic disease which it usually accompanies. —Ed.]

Natural Course. Variability in clinical course, pattern and natural history was stressed.[1984] Unpredictable spontaneous remissions and exacerbations were characteristic. [Failure to appreciate these facts has been largely responsible for unsatisfactory and uncontrolled methods of assessing the efficacy of therapeutic agents in R.A. The recently published book by Short, Bauer and Reynolds (Commonwealth Publishers, Boston, 1957) gives the most comprehensive data yet available on the biography of this disease. In 293 patients observed for over 20 years, the percentage in remission decline from 17.2 to 13.2; that of moderately improved patients increased slightly. Sharp drops occurred in the percentage of cases that were slightly improved or stationary (from 24.3% to 8.6%, and from 26.8% to 2.3%), while the percentage of patients who had deteriorated rose from 19.2% to 62.6%. The majority of these patients had attacks lasting one year or less, and subsequently had either brief or long remissions. In general, the group having an intermittent course spent twice as long in remission as in exacerbation. Though attacks lasting a year or longer were less likely to be followed by a remission, complete remissions did occur in some after from two to five years of active disease.—Ed.]

Diagnostic Criteria. The tentative criteria for diagnosis of R.A. were revised after two years. A new, most stringent category of "classical rheumatoid arthritis," requiring seven criteria, was estalished, and other refinements were introduced.[2588, 2589, 2590] Measuring and recording the activity of R.A. by the "systemic index" and the "articular index" of Lansbury were reviewed.[1808]

Pathologic Characteristics

Although the pathologic morphology of R.A. could not be considered to be specific, rheumatoid lesions were said to be distinguishable from those of dermatomyositis, systemic lupus erythematosus, polyarteritis nodosa and scleroderma, partly by their own characteristics and partly by the absence of various pathologic features dominant in each of these other diseases.[615] Because of diffuse pathologic changes, the term "rheumatoid disease" appeared to be preferable to "rheumatoid arthritis."[698]

Granulomas of the valvular endothelium resembling rheumatoid nodules were again observed.[2820, 2838] Among 100 patients, five showed rheumatoid granulomas in the valves of the heart; one patient had such a lesion also in the myocardium. Nonspecific chronic endocarditis, histologically unlike rheumatic endocarditis, was seen in nine patients and attributed to R.A.; rheumatic fever played no significant part in causing the cardiac lesions of rheumatoid disease.[695] Postmortem examination of a 33 year old male who had a history of rheumatic fever and who developed peripheral R.A. at the age of 21, with involvement of the sacro-iliac joints, and who died of

myocardial failure, showed no cardiac lesions characteristic of rheumatic fever or syphilis. The aortic valve was distorted, the cusps were widely separated, and the supravalvular intima was thickened and partially calcified. Sections showed necrosis of the intima and inflammatory reaction about the vasa vasorum. The adventitial vessels were thickened, and elastic tissue had been destroyed by fibrosis and necrosis.[2015] [Confusion is promoted by failure to distinguish between R.A. and ankylosing spondylitis, which this patient probably had.—Ed.]

The vascular lesions of R.A. showed a variety of histologic characteristics, being indistinguishable in some patients from those of polyarteritis nodosa, yet the similarity of lesions in the blood vessels to those of other connective tissue diseases was not accepted as evidence for common etiology or pathogenesis.[2904, 2906] Vasculitis occurred in subcutaneous nodules, synovial membrane and striated muscle. Arteritis was seen in the meninges, in the perineurium of the peripheral nerves,[2838] in numerous viscera, and in coronary arteries.[2820]

Rheumatoid lesions were further observed in various organs of a high percentage of autopsied patients. In the minority of sites, these lesions were typical granulomas (spleen, larynx, subcutaneous nodules, synovium, tendons). Less characteristic chronic inflammatory changes occurred in pericardium, pleura, liver, spleen, kidneys, lungs, [785, 1244] lymph nodes, perineurium, striated muscles and salivary and lachrymal glands.[697, 849, 2436, 2820, 2838, 3068, 3154] In 14 anterior pituitary glands from rheumatoid patients, there was abnormally low granulation of mucoid cells, but this also occurred in nonrheumatoid controls.[178, 2365] Fibrinoid, a common component of rheumatoid lesions, was described as an acidophylic, homogeneous, refractile material that had the tinctorial properties of fibrin. Histochemical and morphologic characteristics of this substance suggested that it was derived from fibrin.[2215, 2223] However, fibrinoid contained in renal arteriolar lesions of malignant hypertension could be differentiated by staining reactions from "connective tissue fibrinoid."[2182, 2183] Diversely composed fibrinoids were also observed by proteolytic technics.[3194] Also, by the fluorescent-labeled antibody technic, fibrinoid material from patients with R.A. and other connective tissue diseases appeared, at least partly, to be fibrin.[680] Subcutaneous nodules (from patients with R.A.) examined by an antibody technic using fluorescent anti-human gamma globulin evinced specific concentrations of gamma globulin.[3167]

With the elimination of two instances where secondary amyloidosis might have been caused by other factors, there remained six (13.3%) of 47 necropsies on rheumatoid patients over a 19-year period in which amyloidosis appeared to be a complication of R.A. Chemical fractionation, variability in staining reactions, and responses to immunohistochemical testing suggested that secondary amyloid was not a uniform chemical substance,[3070] but contained gamma globulin in considerable amounts,[3166] and comprised a mixture of several glycoproteins, probably derived from serum,[1822] and tending to bind Congo red.[1823, 1824] In 10 of 20 patients, secondary amyloid disease was associated with R.A.; in six of the 10, gastrointestinal roentgenologic examinations disclosed evidence of peptic ulceration.[3222] Amyloid infiltration of the nerve roots produced numbness, weakness and loss of reflexes of the lower limb in a man with R.A.[2278] [Rheumatoid disease is becoming one of the leading causes of secondary amyloidosis.—Ed.]

Laboratory Studies in Rheumatoid Arthritis

Erythrocyte Sedimentation Rate. Observations on several hundred patients who had been hospitalized for R.A. and who were reëxamined after intervals of from five to 10 years suggested than an elevated sedimentation rate on discharge was prognostically less favorable than an elevated sedimentation rate upon admission. The level of sedimentation rate correlated well with functional

capacity, and reflected the course of the disease as more serious in women than in men.[899] [This reported correlation of ESR with functional capacity has numerous exceptions. Satisfactory functional capacity despite elevated ESR is not at all rare. —Ed.] A micromethod was described for estimation of the erythrocyte sedimentation rate with capillary blood.[1914] Review of the differential sedimentation test was based on 30,000 determinations in 27 years. The test, which depends upon electrostatic neutralization of charged colloid particles, appeared to be more sensitive in early cases than did other acute phase reactants, and paralleled more closely the swings in tissue reactivity associated with exacerbations and remissions.[613]

The Westergren method was considered to be the most reliable indicator of the patient's clinical state.[841] However, a normal value was recorded in 33 of 287 patients attending one clinic; 14 of these 33 had signs of "active disease."[2527] [More definite criteria of "active disease" are badly needed, but probably must await further understanding of this disease.—Ed.]

Hematologic Studies. Anemia associated with R.A. was considered to be due to a combination of disordered iron metabolism, marrow dysfunction and diminished red cell survival.[837, 1047, 1568, 2053, 2054] Examination of the bone marrow suggested that the degree of anemia, though related to activity of the disease, did not depend upon a deficiency of iron in the marrow; the cytology of the marrow showed no characteristic abnormality.[2530] [It appears to be established that the anemia in R.A. results from increased blood destruction without adequate compensatory production.—Ed.] A hematologic remission followed splenectomy in patients with Felty's syndrome.[703, 711] Rheumatoid patients eliminated red cells from healthy donors with abnormal rapidity[38] and did not have particularly high plasma volumes.[1567]

Microelectrophoresis was said to define accurately the abnormal protein pattern in rheumatoid sera.[2650] The sera of many patients with rheumatoid and nonrheumatic diseases showed increases in protein and glycoprotein components, due apparently to rises in the carbohydrate-rich globulin fraction relative to the carbohydrate-poor albumin fraction, and also in the carbohydrate content of the alpha-1 and alpha-2 globulin fractions. These phenomena appeared to be related to inflammatory activity, and the level of total serum glycoproteins also varied with the clinical course.[342, 1312, 2976] However, the significance of serum glycoprotein changes and their prognostic value were not thought to be clearly established.[332, 944, 1697, 2438, 2567, 2786]

The serum also contained increased amounts of inhibitors of trypsin and chymotrypsin,[312, 611, 612] and the urinary concentration of acid mucopolysaccharides was higher[773] and that of glucuronides was lower[1472] in patients than in controls. Determination of serum glutamic oxalacetic transaminase levels showed no significant difference between rheumatoid patients and controls.[171] Among the laboratory indices measuring inflammatory activity of R.A., the diphenylamine reaction of Dische (DPA) correlated well with clinical observations.[12, 2787] C-reactive protein could be measured by a latex fixation technic.[2825] The distribution of periodic acid-Schiff-positive substances after electrophoresis on paper strips did not differ in patients from that in healthy controls, and distribution was approximately the same in tests on serum and on synovial fluid. However, rheumatoids, on semiquantitative representation of the results by a planimetric index, ranked higher than did controls.[1622] There was no significant difference in the excretion of total hydroxyproline between rheumatoid patients and normals, either in absolute value or as fraction of total amino acid excreted.[3414]

Synovial Fluid. Characteristics of synovial fluid were related to clinical activity in 53 rheumatoid patients.[1978] Intrinsic viscosity was lower and colloid osmotic pressure higher in fluids obtained from patients in Stages I and II than in those from patients in Stages III and IV. The mean protein glucosamine concentration was higher in patients with slight or no local joint destruction than in patients with marked intra-articular destruction. The mean potassium and protein glucosamine concentrations were higher and the intrinsic viscosity was lower with very active disease than with mild disease. It was suggested that the differences between fluids in early and late stages (pointing toward normal despite progressive anatomic alteration) could represent the subsidence of an acute inflammatory process and the supervention of reparative phenomena. This study further indicated that increase in colloid osmotic pressure of the fluid was due principally to increased protein concentration. Enhanced though perhaps defective synthesis of hyaluronate increased colloid osmotic pressure of the synovial fluid and was the likely principal force in the formation of effusions.

Hyaluronic acid concentration, relative viscosity and intrinsic viscosity were all decreased markedly in R.A., and although there was no evidence of enzymatic degradation, defective synthesis of hyaluronate in rheumatoid synovialis was also suspected.[1874]

An objective record of intra-articular rheumatoid activity could be obtained by estimating the degree of polymerization of synovial fluid mucin through determination of synovial fluid viscosity. However in 119 patients, lack of significant correlation with indices of systematic activity suggested that changes in affected joints probably were not due to a general disturbance of hyaluronic acid metabolism.[889] Tissue obtained at arthrodesis, when the proliferative process had diminished, exhibited some residual oxidative metabolism, while anaerobic glycolysis had returned approximately to normal.[777] Synovial fluid gave a lower incidence of positive hemagglutination tests than did serum.[1768]

Roentgenograms. Radiologic signs of R.A. were described in a comprehensive study of 407 men and 625 women in whom the disease had been diagnosed not more than six years prior to their admission to a hospital in Finland.[2897] Narrowing and erosions in the hands and feet could be detected within two months, whereas, in the knees and ankles, erosions were rare in R.A. of less than five months' duration. Lesions developed more rapidly in women than in men. With arrest, there was reversion to normal of soft tissue changes and of demineralization, and occasionally also of cysts and erosions.[2916] The radiologic diagnosis of R.A. rested on analysis of osteoporosis, reduction of joint space, erosion of joint margins, subluxation and ankylosis; these changes were best shown in films of the hands.[1514] At the IX International Congress on Rheumatic Diseases, 60 experienced rheumatologists examined a series of hand x-rays showing varying degrees of R.A. Inter- and intra-observer opinion differed widely on grading of minimal changes; satisfactory agreement was found on the grading of osteoporosis, but there were wide differences of opinion on the interpretation of erosion.[1670] [This study is of great interest to anyone planning population surveys. —Ed.] A technic for demonstration of soft tissue swelling of the small finger joints in the dorsovolar projection was described.[2898] Decreased mineralization of bone presented problems in diagnosis,[1671] but could be expressed by a system of numerical grading based upon comparison with a set of standard x-rays.[1801] Profound destructive changes of advanced disease (mutilating arthritis) were not considered to be rare;[1647] one such extreme case was reported.[2943]

L.E. Phenomenon in R.A. Some workers[1943] claimed never to have encountered a positive L.E. preparation in this disease, but the majority reported

the occurrence of the L.E. phenomenon in 2% to 19% of rheumatoid patients.[157, 1210, 2343, 2613, 2802] Typical L.E. cells were observed in 25 of 91 patients with typical R.A., and more frequently in those with nodules and elevated gamma globulin levels or with Felty's syndrome.[1062] Among 488 rheumatoid patients, the incidence of L.E. cells was 17%.[1713] [Positive L.E. preparations may be obtained by various technics executed with care to avoid damage to cells. The serologic and nosologic significance of these observations is not clear. For practical purposes, a clinical diagnosis of R.A. should not be invalidated by a positive L.E. test; but a strongly positive L.E. test furnishes presumptive evidence against R.A. in a clinically undifferentiable problem.—Ed.]

Tests for Rheumatoid Factor. A test employing sheep serum to potentiate the agglutinating activity of rheumatoid sera against sensitized sheep erythrocytes gave positive results in 62% of 331 patients. Rarely, rheumatoid factor was detected within 24 hours of the onset of joint complaints. [This observation is contrary to the experiences of most of us. Probably present before joint symptoms. —Ed.] Usually the incidence of positive reactions increased with the progression and the debilitating effects of the disease. The reaction was positive in a high percentage of patients with nodules, did not vary greatly with response to therapy, and could be concurrently obtained in joint fluid with the same or even higher titer.[1550] Since the agglutinating factor of rheumatoid serum had been located in serum globulin, tests were performed with the cold-precipitable fraction, and yielded positive results in 95% of patients.[3020, 3021, 3022, 3023] With the euglobulin fraction of serum, positive results were reported in over 90% of 133 tests in 108 patients with R.A.,[3412] while only 2 to 7% of 162 tests in 150 control subjects gave positive reactions. A further procedure for measuring inhibition of positive rheumatoid sera by the euglobulin fraction was described. The serum euglobulin of 105 patients with R.A. failed to show inhibition in 100% of the cases, while over 96% of the euglobulin fractions of control subjects caused inhibition. The test was technically difficult and not readily adapted to routine laboratory facilities.[3418]

The latex fixation test, consisting of the agglutination of polystyrene latex particles coated with pooled gamma globulin,[2824] was adapted to a slide test,[2823] and described as a simple screening procedure with good sensitivity and specificity for the serologic diagnosis [or confirmation—Ed.] of R.A.

A three-step method for the diagnosis of R.A. yielded positive results in 99.4% of 582 patients with known R.A., and in 5.2% of controls. The first step consisted of latex agglutination in the presence of pooled human gamma globulin. If no agglutination occurred, the euglobulin fraction of the unknown serum was tested by the latex fixation method. If agglutination still failed, the euglobulin inhibition test was performed. The series of tests was said to be practical for routine use, although it required meticulous attention to detail.[1301]

The latex fixation test was developed into a "one tube technic," which utilized a patient's own gamma globulin obtained by ammonium sulfate fractionation; this was an improvement over alcohol fractionation or cold dialysis.[2826]

A flocculation test was devised, utilizing bentonite particles of selected size which had been sensitized by human gamma globulin (Fraction II); it gave positive results in 78% of adult patients with definite R.A., in 2% of controls, and in none of normal subjects. There was excellent agreement of this simple and rapid method with the sensitized sheep cell agglutination test.[361] Numerous

other modifications, analyses and clinical assessments of the several tests for rheumatoid factor were reported.[158, 159, 177, 388, 442, 609, 679, 745, 963, 1131, 1171, 1389, 1608, 1769, 1781, 2101, 2313, 2364, 2397, 2409, 2520, 2591, 2617, 3062, 3082, 3160, 3293] [From the accumulated data it is evident that the agglutination reaction is frequently manifested by sera of adult patients with definite peripheral R.A., but also by sera of patients with macroglobulinemia associated with a variety of other rheumatic and nonrheumatic disorders. The expectation of a test wholly specific for R.A. has not been realized, but the several laboratory determinations for rheumatoid factor have practical diagnostic value in association with other clinical data. More importantly, investigation of the characteristics of rheumatoid factor has led to provocative clinical and immunochemical correlations.—Ed.]

On ultracentrifugation, rheumatoid serum yielded a high molecular weight protein that had a sedimentation constant of approximately 22 S, and that could be dissociated into two fractions, one of which had a sedimentation coefficient of approximately 19 S. This abnormal protein was present in the gamma globulin fraction of serum and joint fluid, and was related to the intensity of the sheep cell agglutination reaction and the latex fixation test.[1037, 1039] These factors were proteins closely related to other 19 S gamma globulins and to the 19 S antibodies, complexed in serum and plasma to another type of protein, since precipitates formed by interaction of fraction II gamma globulin and rheumatoid factor readily yielded highly active 19 S material both by dissociation of the 22 S complex and by centrifugal isolation.

The substance in gamma globulin which reacted with rheumatoid factor in the F II precipitin and F II tanned sheep cell agglutination tests was concentrated by precipitation with sodium sulfate.[549] In this form it consisted of polydispersed molecular aggregates of gamma globulin with S 20 constants as high as 40, as well as of inhomogeneous aggregated material. The aggregate precipitated readily with rheumatoid factor, regardless of the reaction volume. In low concentration it inhibited the F II reaction and sensitized tanned erythrocytes to the agglutinating action of a positive rheumatoid serum. On the other hand, nonaggregated gamma globulin (7 S) did not precipitate with rheumatoid sera, and in low concentration did not inhibit the F II tanned sheep cell agglutination reaction or sensitize tanned erythrocytes. Nonaggregated gamma globulin in large excess inhibited the precipitin reaction of aggregated gamma globulin with rheumatoid factor. Essential differences were noted between these serologic systems which did not involve immunologic reactions and others which did (sensitized sheep cell test, Rh-sensitized system, reaction of rheumatoid factor with immune precipitates).[549]

A precipitation reaction occurred between serum of rheumatoid patients and human gamma globulin, giving a positive F II test.[924] Upon addition of gamma globulin (F II) to the serum of most rheumatoid patients, precipitates formed which were correlated with the titer of F II agglutination of the serum. A quantitation of these phenomena indicated that precipitation depended upon the F II titer, the particular lot of F II, and the volume in which the reaction took place. It was therefore suggested that rheumatoid factor and F II coexist in serum.[925, 926] Gamma globulin (F II) reacted similarly, as either a sensitizing or an inhibiting agent, in various systems tested for rheumatoid factor, whether the globulin fraction was derived from rheumatoid or nonrheumatoid subjects. The agglutinator and its globulin reactant, or a precursor, were found to coexist in rheumatoid sera, and it was confirmed that gamma globulin had an increased affinity for rheumatoid factor after heating to 63° C. for 10 minutes.[388, 1989]

Rheumatoid factor was purified and characterized as a macroglobulin mixture.[847, 1392, 1942, 3163, 3164, 3193, 3211, 3321] Reducing agents specific for the disulfide linkage polymerized its macroglobulins but did not affect the 7 S component.[1391] In the sera of 240 R.A. patients the euglobulin fraction containing the agglutinating factor was

examined for polysaccharide content, which in 103 instances proved to be greater than 25 mg.% of original sera. In the latter group the hemagglutination test was rarely positive, but in the former it was positive in the majority of instances.[2880] Unlike the protein responsible for L.E. cell formation, rheumatoid factor did not pass the placental barrier.[2328]

The possible relation of rheumatoid factor to complement or the C'4 constituent of complement was suggested,[2789, 3318] but there was no consistent correlation between agglutination titer in rheumatoid sera and complement; moreover, inactivation of complement by various means did not destroy rheumatoid factor.[1264, 1833] It was therefore proposed that rheumatoid factor represented an additional accessory element to antigen-antibody systems, different from complement or conglutinin.[1267]

Other Serologic Studies. Among immunologic reactants of investigative interest were iso-agglutinins to leukocytes in rheumatoid sera,[1716] and an antigen prepared by acetamide extraction of Type III, Lancefield Group A *β hemolytic streptococci.*[211] However, sera from patients did not differ from that of normals in the titer of antibody to autoclaved streptococci Group A.[1228] Haptoglobins were increased in 33 rheumatoid patients, but the change did not appear to parallel titers of rheumatoid factor.[46] From rheumatoid plasma, cold-precipitable globulins were recovered in increased amounts, and were apparently bound by chondrotin sulfate added *in vitro* to the plasma. These globulins also occurred with inflammatory diseases other than rheumatoid arthritis.[1696] Variable increases in the titers of sheep cell agglutinating factor, anticomplement, antistreptolysin, and antistaphylolysin were noted in sera from patients with hypergammaglobulinemia with diverse causes, such as R.A., purpura, polyarteritis nodosa, myositis, cirrhosis of the liver and systemic lupus erythematosus.[3201]

It was demonstrated that human blood groups could be further differentiated serologically, namely, by an agglutination inhibition test in which rheumatoid sera agglutinated Group O Rh-positive red cells coated with select incomplete anti-Rh antibodies.[1264, 1266] The inhibitor resided in the gamma globulin fraction, and the two glood groups were designated phenotype Gm (A+) and Gm (A−). These groups were not correlated with sex, pregnancy, various other blood group factors or haptoglobins, but were found to be hereditary and distributed among 360 healthy Swedish adults in 59.7% and 40.3%, respectively, according to Mendelian principles.[1265, 1267, 1268]

A complement fixation reaction between human sera and antigens derived from various human organs served to detect complement-fixing reagents in the sera of patients afflicted with varied acute and chronic ailments, including six with R.A. Three of these were positive to human kidney antigen and three negative to both liver and kidney antigens.[1093, 1966] The globin component of hemoglobin agglutinated coccal and especially streptococcal antigens, and such agglutinations were inhibited by various protein and mucopolysaccharide fractions from connective tissue and sera of rheumatoid patients and others.[3097, 3098, 3099]

Etiology and Pathogenesis

That the cause of R.A. remains disconcertingly unknown has been somewhat mitigated by current efforts and advances in comprehending the natural course of the disease, its epidemiologic features, and its associated morphologic and physiochemical changes.

Factor of Infection. An attempt to isolate a virus from biopsy material of synovial membrane of two rheumatoid patients gave negative results.[576] The assumption that *Bacterium parasiticum* had a role in the causation of R.A.[220] remained unproved. Though the most likely current hypothesis was of a micro-

bial or an immunopathologic etiology, no direct substantiating evidence for the former was available. The postulate of a hypersensitivity reaction in the pathogenesis of R.A. was stimulated by the resemblance of some of its pathologic features to experimental lesions of serum sickness, i.e., focal degeneration of collagen, infiltration by lymphocytes, and the presence of fibrinoid and vasculitis. Consistent with the hyperergic theory was the elevation of serum gamma globulins in many rheumatoid patients. However, arthritis was reported in patients with agammaglobulinemia of the congenital type, or with acquired dysgammaglobulinemia.[1560] In two of three cases, arthritis followed the clinical onset of agammaglobulinemia; the third patient had a congenital deficiency of gamma globulin, and developed severe joint disease at the age of three years.[1194] One of these patients had complete remission of joint symptoms during an attack of viral hepatitis with jaundice. Although these observations rendered untenable a pathogenetic theory for which gamma globulin or circulating antibody was essential, they showed that agammaglobulinemic patients could develop a bacterial type of hyperergia. Thus, extreme states of hypogammaglobulinemia occurring spontaneously or congenitally, and not infrequently complicated by inflammatory disorders of connective tissue, provided a natural experiment in the pathogenesis of arthritis. None of four patients with the acquired, and of eight with the congenital type of agammaglobulinemia, showed evidence of either rheumatoid agglutinating factor or inhibition of agglutination.[3165] Although six of these patients had polyarthritis with some clinical features of R.A., the identity was considered to be equivocal: the arthritis tended to be asymmetric; narrowing of the joint space was seen in only one instance; demineralization of bone was generally not a prominent feature; and none of the patients had subcutaneous nodules or such progressive changes in skin, muscles and blood vessels as are found in R.A. [We agree that the nosologic problem should remain open.—Ed.]

Demonstration of rheumatoid factor by several tests depending upon immunologic mechanisms has been construed as *prima facie* evidence for hyperergic pathogenesis of R.A. Although antibodies were commonly identified with gamma globulins of the type represented in rheumatoid factor, and such proteins could be localized in rheumatoid lesions by microfluorescence,[2106, 3168] a typical reaction also occurred in a nonimmunologic system, resulting, perhaps, from physicochemical aggregation with antigen-antibody complexes.[549] Rheumatoid patients with advanced active disease and subcutaneous nodules did have large amounts of 22 S protein complex in their sera. However, it was speculated that, apart from any immunopathologic significance of macroglobulins, this association might denote a direct precipitation of unstable protein complexes in certain organs, giving rise to subcutaneous nodules, polyarteritis and perhaps splenomegaly. The latter could also represent hypertrophy, a function of increased gamma globulin production.[1038]

Factor of Electrolyte or Endocrine Imbalance. In further metabolic studies, the activity of R.A. could not be correlated with changes in electrolytes, calcium, phosphorus or nitrogen balance.[570] Peroral potassium tolerance tests showed no difference between serum potassium levels of rheumatoids and of controls,[1618] but in some rheumatoids the potassium concentration in erythrocytes was increased.[1747] It was pertinent to the clinical and largely unexplained observation of diffuse edema in R.A. that the extracellular fluid phase in 40 patients, as measured by the thiosulfate method, was clearly increased over that in 10 controls, and the increase was correlated with

advanced disease.[1615] In 25 rheumatoid patients, urinary excretion of 2,5 dihydroxyphenylpyruvic acid indicated a disturbance in intermediary metabolism of phenylalanine and tyrosine.[2280] The lactic acid response to muscular exercise in 11 rheumatoid patients was almost identical with that of controls.[1616] Although by the bromsulfalein and coproporphyrin tests, abnormal liver function was found in 23 to 30% of rheumatoid patients,[723] there was no convincing evidence of a fundamental hepatic dyscrasia in R.A.[817]

While earlier reports based on routine clinical studies failed to show a disturbance in thyroid function of rheumatoid patients, the possibility of an association between R.A. and thyroid disorder was restated by Short, Bauer and Reynolds.[1333] A thyrohypophysial syndrome was postulated for some rheumatoid patients. Clinical manifestations included edema of the lids, obliteration of the frontal palpebral sulcus, malignant exophthalmos, facial and temporal edema, and localized myxedema. Though such criteria were admittedly subjective, this syndrome was found in 44% of 148 rheumatoid patients (77 women and 71 men), and in 10% of a control group of 100 patients (81 women and 19 men).[1619] Tenderness of joints, with typical morning stiffness, history of joint swelling of "considerable" duration without improvement, and a history of medical care for these symptoms had occurred in 8% of 524 thyroidectomized patients, in 3.8% of 484 cholecystectomized patients, and in 4.3% of 900 controls. In most instances, thyroidectomy had had an aggravating effect upon these symptoms.[1614] [Myalgias, arthralgias and arthropathy are more frequent in the patient with hypothyroidism than these statistics reflect (O.S.).—Ed.] Possible imbalances of adrenal hormones and of pituitary-adrenal homeostasis were again investigated. Reversal of the urinary excretion ratio of noradrenalin : adrenalin in some rheumatoid patients indicated enhanced destruction of noradrenalin by "L" amino-oxydase, leading to decreased or suppressed urinary noradrenalin.[2129] Clinical equivalents of this observation in hypotension, muscular atrophy, intolerance of carbohydrates, cutaneous hyperhidrosis, bone atrophy and capillary disorders, and the presumed overactivity or quantitative increase in "L" amino-oxydase, suggested a link between spontaneous rheumatoid arthritis and the hydralazine syndrome. Values for urinary excretion of 17-hydroxycorticoids and 17-ketosteroids varied somewhat among ambulant patients, hospitalized patients, male and female patients and controls, as well as in diurnal phases, but did not prove a deficiency in cortical hormones.[266, 1434, 2306, 2374, 3225] Morphologic changes found in the anterior pituitary glands of patients, and consisting of undergranulation of mucoid cells, were also seen in nonrheumatoid controls.[178, 2365]

Psychogenic Factors. Rheumatoid patients appeared to be more "intropunitive" than did controls.[2220] To test a theory of disease-specific psychosomatic responses, rheumatoid patients were exposed to psychologic stress; their muscular tension did not differ much from that of patients with peptic ulcer. Both groups showed evidence of conflict over dependence, and neither of conflict over aggression. Historical data indicated that, in childhood, rheumatoid patients might have had more strained relations with their parents, especially with their mothers.[2919] R.A. was rare among mental patients.[2398] Only one case of active R.A. during a decade was seen among 4,500 psychotic patients.[892] [This has not, however, been the object of wide attention.—Ed.] Epidemiologic screening technics applied to R.A. suspects revealed the prevalence of certain psychosocial problems or characteristics: in male patients, these were low income, low education and termination of marriage; in female patients, the most striking associations were with low education, having four or more children, reporting no spare time in the third decade of life, and worrying more than other people.[1722] In the opinion of the authors of one report, "R.A. is a stress disease and represents a

maladaptation to psychobiological stress." [This is easy to say but difficult to prove.—Ed.]

The possible role of the vegetative nervous system in the pathogenesis of R.A. did not receive much attention; "autonomic dyspraxia" was said to induce R.A. and related diseases.[1379] [Previous studies have indicated that vasomotor instability is a common feature, occurring in about 75% of rheumatoid patients, but there is no evidence that autonomic or vasomotor imbalance has anything to do with the cause of R.A.—Ed.]

Factor of Heredity. The tendency to a familial aggregation of R.A. was confirmed.[75, 1333, 2743, 2744] That incidence of positive serologic reactions was from four to five times higher among persons consanguineous with patients than among controls added to the possible genetic significance of the familial trend.[1837, 3415] The published reports on 29 pairs of identical twins, one or both of whom suffered from typical R.A., were reviewed; in only 45% of the pairs had both twins acquired the disease.[577] Another pair of identical twins living remote from each other had the onset of R.A. at the ages of 53 and 59, respectively, in similar clinical evolution.[1262] In a preliminary report of a long-term study of R.A. in twins, observation of 29 pairs revealed that, of 14 monozygotic pairs, three showed concordance and 11 showed discordance, and that, of 15 dizygotic pairs, one showed concordance and 14 showed discordance.[3102] While the total evidence for hereditary predisposition was only suggestive, Stecher[2945] considered this factor to be operative together with other pathogenic influences. He calculated that gene frequency and penetrance were low, so that 1.2% of the population were susceptible to R.A., and one-half of that fraction developed the disease.

Relationship to Other Diseases

In view of divergent clinical manifestations and different reactions in the sheep cell agglutination system, as well as of radiologic and pathologic criteria, it appeared to some that ankylosing spondylitis was an entity distinct from R.A.[1017, 1130, 2062, 2762] [Most observers in this country agree. The only evidence with any validity offered in support of a common etiology of ankylosing spondylitis and rheumatoid arthritis is that the histologic sections of synovium in these diseases cannot be differentiated with certainty. Placing diagnostic significance on synovial histology which may present similar appearances in some cases of R.A., ankylosing spondylitis, osteoarthritis, and arthritis due to infection has repeatedly proved to be fallacious. In contrast, the only pathognomonic hallmark of rheumatoid micropathology, the necrobiotic granulomatous nodule, does not occur in ankylosing spondylitis. The striking difference in sex incidence, the absence of serologic differences in clinical features, and the natural history and complications point strongly to separate and distinct identities of these two diseases. It is strongly recommended that these diseases be clearly distinguished and not grouped together in future reports. The evidence has become too strong to ignore, and the onus of proof now lies with the proponents of the common identity of these diseases.—Ed.]

The majority of 42 patients with psoriasis and arthritis had notably erosive articular lesions, with a predilection for involvement of the distal phalangeal joints associated with psoriatic changes of the nails, but also a high incidence of sacro-iliac joint involvement. Severe crippling was rare, and 94% of this group had a negative sheep cell agglutination test;[3372] this type of polyarthritis was separated from R.A.[1918, 3373] Involvement of the terminal interphalangeal

joints was much more common in psoriasis (52%) than in patients with R.A. alone (11%). An additional distinguishing feature was erosion of the tips of the terminal phalanges.[3374] The coexistence of clinical R.A. and polyarteritis nodosa was again reported;[996] these two syndromes could not always be distinguished.[2457] Observations on 37 patients with arthritis and polyarteritis nodosa were reported.[458] The arthritis associated with ulcerative colitis tended to be recurrent, mild and often migratory. Radiologic changes in some joints did not differ from those seen in R.A., but negative agglutination reactions and differences in clinical course suggested an essential difference from R.A. Arthritis was a complication of ulcerative colitis in 20%[1426] to 22% of patients.[1731] Among 61 patients with chronic ulcerative colitis, arthritis occurred in 12 and appeared to be of the rheumatoid type. Of 48 children with ulcerative colitis, eight had arthralgia or polyarthritis, usually with hydrops; large joints were usually involved.[1797] Intermittent hydrarthrosis (periodic benign synovitis) was a manifestation of R.A. in some instances.[918]

The differentiation between R.A. and systemic lupus erythematosus (S.L.E.), formerly considered only on clinical and pathologic grounds, was supported by additional evidence from immunochemical data. It was established that the macroglobulins of the rheumatoid factor differed from the 7 S macroglobulins of the L.E. factor. Typical L.E. cells occurred in only a small percentage of rheumatoid patients,[1210] and serum complement levels in S.L.E. were lower than in normals.[3318] The umbilical cord blood of a pair of twins contained L.E. factor but not R.A. factor, though both were present in the serum of the mother, who had R.A.[1914] The Rose test was also negative in the cord blood of six children, each of whose mothers had R.A. with positive Rose tests. Although any rheumatoid patient with typical L.E. cells was considered to have S.L.E.,[185] the majority of contributors agreed with Goslings[1210] in recommending that diagnoses be decided by comprehensive data, rather than by one criterion.[1858, 2343] [The A.R.A. diagnostic criteria also compromise this issue by excluding from R.A. any patients showing four or more L.E. cells in two smears from heparinized blood incubated not over two hours. To contribute to uniform diagnoses studied by different workers, this exclusion is warranted. It is an arbitrary assumption, which will exclude a certain number of people who have R.A. and not S.L.E. Whether these are two diseases, or one with variable manifestations in different patients, cannot be determined with finality at present.—Ed.]

Resembling R.A. in the distribution of severely destructive articular lesions, reticulohistiocytosis was found in six more patients.[2180, 3228] This rare disorder was manifested by sheets of yellow-brown papules over the dorsal aspect of hands and fingers, the face and forearms, by xanthelasma palpebrarum and by swelling of tendon sheaths. The nodules and synovialis showed giant cells, with abundant granular cytoplasm which was thought to contain a lipoid polypeptide complex. [A differential radiologic feature is the well delineated segmental destruction across some phalanges. It is unlikely that this rare disease and R.A. are identical.—Ed.] R.A. was associated with endocardial fibroelastosis.[2014] A symmetric polyarthritis indistinguishable from R.A. was reported with various visceral malignancies.[3006] Joint pains occurred in 11 of 26 patients (42%) with a severe form of hepatic cirrhosis; in three of these the joints resembled those in typical chronic R.A.[202] [Further observations suggest that these patients had a less well recognized and possibly uncommon feature of S.L.E.—Ed.] Joints most commonly affected were the ankles and wrists. A possible rheumatic pathogenesis was suspected in a patient suffering from diffuse chondromalacia, generalized

chrondritis, perichondritis and iritis.[1366] [The term "rheumatic pathogenesis" is misleading and vague.—Ed.]

Juvenile Rheumatoid Arthritis

Despite some distinctive clinical features and a lower incidence of seropositivity, the disease of patients in this group was generally considered to be the same as adult R.A. Edström reported on 161 patients with juvenile rheumatoid arthritis treated since 1936 at the University Hospital, Lund, Sweden.[886] The incidence of R.A. appeared to be lower in children than in adults (5 to 7% of all rheumatoid patients); twice as many females as males were affected; the peak incidence occurred during the second and third years of life. Still's triad was present in only seven patients.

Juvenile R.A. differed clinically from the adult type in a more common occurrence of (a) ankyloses (especially of the cervical region),[886, 1951, 3417] (b) iridocyclitis (6% of 200 patients),[2848, 2849] and (c) skin eruptions (28% of 166 patients).[1173, 1520] Sheep cell agglutination tests were positive in 50%,[465] and 10%,[1252] but more often in children with cervical arthritis tested directly with euglobulin fraction or by the inhibition test.[3417]

Height was temporarily more than 10% below normal in about half of 119 children, but growth was rapidly resumed in many when the disease became quiescent; weight was lost at the onset, remained low during disease activity, and resumed normal levels with quiescence.[91] Abnormalities of bone development included premature epiphysial fusion with shortening, temporary decrease or arrest of bone growth, dense metaphysial bands, and subchondral bony outgrowths of the epiphyses. Cortisone therapy over prolonged periods produced the usual temporary obesity and a slowing of growth in height at all but minimal levels of dosage. There was little apparent effect on skeletal maturation.[91]

Prognosis appeared to be better than previously reported.[1252] A 20-year follow-up of 85 children found 62% to be symptom-free, 19% well but with residual disease, 6% with active disease, and 13% incapacitated or dead. The minority with fully developed Still's syndrome had fared worse.[884, 886] Transitory and/or localized disturbances of growth attributable to juvenile R.A. occurred in about half of the patients in the series from Sweden and Columbia Presbyterian Hospital in New York. The general principles of management, including use of adrenal cortical steroids (prednisone or prednisolone), were summarized.[1109, 1183, 1186, 3315]

Treatment of Rheumatoid Arthritis

General Principles and Evaluation (Patient Orientation). The natural history of rheumatoid arthritis, tending to intermittent exacerbations and variations with individual patients, has been discussed at length during the last 10 years. The cause of spontaneous remissions is as mysterious as is the etiology of the disease. Prognosis for a single patient is difficult or impossible to determine, except in general terms. Spontaneous remissions of varying duration are most frequent within the first two years of onset of the disease. Despite these facts, many uncritical views prevail concerning the influence of certain clinical regimens or pharmacologic agents on the course and/or outcome of rheumatoid arthritis. Such evaluations were presented without adequate charac-

terization of the patients. In the majority of such reports, no information was provided regarding diagnostic criteria, disease duration prior to therapy, objective methods of assessing disease activity, response to therapy, or duration of this response. Statistical appraisals of results presented under such circumstances have little scientific meaning, and will not mislead the enlightened reader. They are merely clinical impressions that are most often flavored by preconceived notions and limited scope and appraisal.

Unproved assumptions continued to be presented as facts. For example, claims that the muscle atrophy associated with R.A. is due to spasm, that continuous splinting relieves spasm and prevents atrophy,[3029] and that rest and intermittent splinting prevent articular destruction[2586] are clinical impressions rather than established facts. [Most physicians in the field of rheumatic diseases feel that continuous splinting should never be used, as it augments muscular atrophy. Intermittent splinting a few hours per day, for rest and prevention of contractures, is all that is advocated. Cartilaginous destruction, if it is to occur, cannot be prevented by splinting.—Ed.]

The consensus is that therapy for rheumatoid arthritis is best discussed in terms of general management of all aspects of the patient's life. Modifications of his physical and emotional activity and surroundings, use of pharmacologic analgesic and antiphlogistic agents and carefully controlled physical therapy were important. Apparently no specific dietary factors influenced the disease process. All agreed in general terms that "adequate" rest and a good nutrient diet were essential, and that careful, compassionate orientation of the patient by the physician concerning the nature of his disease was absolutely necessary for adequate management.

There are *no* pharmacologic agents presently available that have been proved to prevent the ultimate destruction of joints if this is to occur. Therefore, the choice of analgesic and antiphlogistic agents to be used depends upon the presenting symptomatology. If this can be altered by agents with minimal toxicity, there is no need to administer more potent and more toxic medications. The following articles reviewed the general approach, some with care, precision and critique.[133, 194, 408, 409, 463, 739, 919, 974, 1069, 1070, 1071, 1156, 1217, 1302, 1433, 1451, 1457, 1623, 1700, 1701, 1879, 2228, 2254, 2456, 2480, 2586, 2801, 2947, 3125, 3229]

Analgesics. Salicylates continued to be widely used because their clinical effectiveness, though rarely completely satisfactory, was associated with minimal complications. The antiphlogistic action of salicylate compounds was again demonstrated in rats subjected to injection of chemical irritants into the hind paws.[1657]

Physiologic effects of salicylates in animals and man were studied. Salicylates were shown to produce a distinct, measurable increase in myocardial contractility, but this was minimal when compared to that from digitoxin, sympathomimetic amines, xanthine, calcium and barium.[3220] That salicylates increased the utilization of oxygen and production of CO_2, with effects comparable to those of 2–4 dinitrophenol, suggested their interference with the production of high energy phosphate by oxidative mechanism, i.e., by uncoupling oxidative phosphorylization.[81, 1068, 1983, 2498] There was a general parallelism between anti-inflammatory effect as measured by inhibition of erythema induced by chemical irritants in animals to the increased O_2 uptake, and uncoupling of oxidative phosphorylization. The inconsistency here was that 2–4 dinitrophenol, the classic agent for uncoupling oxidative phosphorylization, is not anti-inflammatory.[16]

Conflicting results of studies designed to show that the anti-inflammatory effect of salicylate was mediated through the pituitary-adrenal axis were reported.[507, 799, 800, 843, 1415, 3096, 3157] Animal findings could not be transferred to man. An excellent study,[2385] using classic endocrine technics in man, was summarized as follows: "The administration of salicylates to normal subjects and to patients with rheumatoid arthritis did not significantly alter the plasma concentration of hydrocortisone and corticosterone, or the urinary excretion of 17-ketosteroids. The administration of moderate doses of salicylate for a few days produced no alteration in the urinary excretion of corticoids, rate of metabolism of infused hydrocortisone or corticosterone, or the rate of synthesis of hydrocortisone by the adrenal cortex. Salicylate was found to evoke a satisfactory anti-rheumatic response in a patient with rheumatoid arthritis whose adrenal cortical function had been markedly or completely suppressed."[2385]

Various preparations were used to test whether buffered salicylate compounds were absorbed more rapidly than nonbuffered salicylate.[189, 506, 563, 689, 959, 2639] Results were inconsistent. These are best summarized by stating: "The difference in the plasma levels of salicylate at ten minutes between the various buffered and nonbuffered aspirins is of small magnitude and of no clinical significance regarding treatment of patients with rheumatic disease—as by one hour there is no difference in serum levels."[657] A comparative double-blind study of 160 patients on buffered and unbuffered aspirin showed that "the time required for analgesia, the degrees of analgesia and the frequency of gastrointestinal intolerance were identical with both preparations . . . antacids serve no useful purpose as constituents of the tablets studied and inclusion of them with acetylsalicylic acid offers no advantage over aspirin alone."[188] Enteric-coated aspirin was reported to be equally effective, and did not cause gastric irritation.[1147, 2928] The distribution of salicylate in tissue of rats using C^{14} carboxyl-acetylsalicylic acid was studied. Thirty minutes after oral administration, the highest levels were found in lung and kidney and the lowest in red blood cells and brain. In rats, 92.3% was execreted in 48 hours, and absorption proceeded at a fixed rate.[345, 676]

Occult gastrointestinal bleeding and acute gastric hemorrhage were reported frequently in association with salicylate administration.[51, 417, 1114, 1677, 2704, 3011, 3014] [The role played by salicylates in the production of acute gastrointestinal hemorrhage and peptic ulceration has not been settled. Investigators came to different conclusions concerning this relationship. The difficulty seems to lie in the selection of suitable controls.—Ed.] Alteration of the prothrombin time was associated with the administration of aspirin in normal individuals[1656] and in patients with cirrhosis of the liver.[1805]

Many allergic phenomena were associated with the administration of salicylate, and included asthma, rhinitis, urticaria, atopic dermatitis and migraine.[253, 410, 523, 1128, 3216] Edema, focal hemorrhage and neural cell damage due to salicylate were reported.[664] A nonfatal case of salicylate toxicity was described.[2684] Methyl salicylate applied locally had some value in increasing range of motion of an involved joint.[423] [This conclusion was based on inadequately controlled observations.—Ed.] Combinations of salicylates, phenylbutazone and corticosteroids in treatment of rheumatoid arthritis were reported.[273, 2361, 2405] The Empire Rheumatism Council's multi-clinic study of patients with R.A. treated by aspirin and by cortisone over three-year[459] and four-year[2098] periods indicated no significant difference in the comparative therapeutic effects of these two drugs. About one fourth of each group were in remission, one fourth of each group were un-

improved, and one-half of each group showed continued activity. Radiologic deterioration occurred in both groups. It was considered that aspirin was of superior value in the management of rheumatoid arthritis because of its lower toxicity. [The degree of functional ability and comfort was not evaluated in this study; there was no expression of how the patient *lived* during the period of therapy, whether in comfort or misery, whether ambulatory or bedridden. Factors of dosage and other clinical therapeutic variables are difficult if not impossible to standardize. Many English and American workers are actively engaged in developing better methods to evaluate critically the therapeutic results of new agents in patients with R.A. Most of us are of the opinion that adrenocortical steroids, artfully administered, are valuable therapeutic agents and superior to aspirin.—Ed.] A small study in juvenile rheumatoid arthritis patients led to the same conclusion after one year's trial.[90] Editorials commenting on these trials were published.[69, 862, 863]

Phenylbutazone. Phenylbutazone was used without serious toxicity in 222 patients with rheumatoid arthritis. Classification of the type of patient, with an attempt to measure objective changes, was carried out in 49 patients treated for from two to five years. This study reported that 39% of these patients found phenylbutazone to be a long-term satisfactory agent. No change in the natural progressive destruction of joints was observed.[2879] A controlled study was carried out in 82 patients with R.A. through use of phenylbutazone and a placebo, each drug being allocated by random case selection. Functional capacity was significantly better and rheumatoid activity less in the cases treated with phenylbutazone than in the controls. Fatal hazards were reported with prolonged use.[875] To avoid severe reactions, the following precautions were suggested: the drug should not be given to patients over 65 years of age, or to those with chronic disorders of blood, alimentary, cardiovascular or urinary system; the dose should not exceed 400 mg. daily (for most patients, 300 mg. was sufficient); the drug should be withdrawn as soon as toxic effects appear; and ineffective trials should not last longer than seven days.[1684] [We agree with these precautions, although this drug may not be absolutely contraindicated for *everyone* over 65 years of age without other contraindications.—Ed.] Clinical effectiveness was greatest in rheumatoid (Marie-Strümpell) spondylitis; less than 50% of patients with peripheral joint rheumatoid arthritis obtained benefit. Incidence of toxicity varied from 4 to 8% of selected patients.[1006, 1221, 1574, 2010, 2089, 2554, 3113, 3184, 3428] If no benefit resulted within one week on doses of at least 400 mg./24 hours, further therapy was usually ineffective.[2010] Intra-articular phenylbutazone proved ineffective in rheumatoid arthritis.[2263] A review of the pharmacology of phenylbutazone,[3115] and studies[1195] showing that phenylbutazone does not act through the "pituitary-adrenal" axis, were reported.

The recent literature contained many reports of the varied toxic effects ascribed to phenylbutazone, including eczematoid dermatitis,[2342] depression of erythropoiesis,[3033] agranulocytosis,[1559] aplastic anemia,[3169] myocarditis,[1447] uremia and hemorrhagic complications,[1318] toxic hepatitis,[94] neovascularization of the cornea,[2482] and nausea.[1005] Development of peptic ulcer, or re-activation of quiescent peptic ulcer, appeared to be a frequent and serious complication.[17, 875, 1221, 2455] The effects of phenylbutazone on gastric secretion and ulcer formation in rats with pyloric obstruction were identical, whether the intramuscular or oral routes of administration were used; ulcer formation occurred, however, without increasing gastric secretion.[1617] Phenylbutazone inhibited gastric secretion in

guinea pigs when administered by the intraperitoneal route.[3241] In man, the effect of phenylbutazone on gastric secretion was not prevented by vagotomy.[1730] Phenylbutazone acutely depressed the 24-hour I^{131} uptake by the thyroid, but this tended to return to normal if therapy was continued over long periods of time. Phenylbutazone blocked the organification of iodine in a manner similar to that of thiourea compounds.[513] Thyroid-stimulating hormone (TSH) blocked the depression of I^{131} uptake by the thyroid gland attributed to phenylbutazone.[1905] Phenylbutazone enhanced the effects of dihydrotachysterol overdosage in rats, increasing soft tissue calcification.[2739]

A patient with rheumatoid (Marie-Strümpbell) spondylitis who consumed 10 gm. of phenylbutazone orally at a single dose developed leukocytosis, followed by toxic degenerative bone marrow changes, intrahepatic biliary obstruction and relapse of an ulcer with hematemesis.[3368]

Cortisone, Hydrocortisone, Newer Steroids and Corticotropin (ACTH) in Rheumatoid Arthritis

There was general agreement on the clinical effectiveness of certain corticosteroids in partial suppression of manifestations of rheumatoid arthritis.[194, 335, 525, 650, 735, 1161, 1219, 1402, 1451, 1460, 1462, 1486, 1555, 1601, 1664, 1791, 1880, 2292, 2416, 2601, 2675, 2676, 2677, 2924, 2977, 3094] The effectiveness of prednisone and prednisolone was confirmed.[275, 324, 325, 682, 956, 998, 1356, 2100, 2179, 2563, 3226, 3291] Other effective steroids included triamcinolone,[1052, 1358, 1364, 1365, 2064, 3429] methylprednisolone[260, 488, 1569, 2088, 2262, 2606, 2895] and dexamethasone.[321, 327, 438, 2927]

Reports of the Medical Research Council and Nuffield Foundation and the Empire Rheumatism Council indicated no significant difference in results of treatment between two groups of patients, one on cortisone and the other on aspirin. However valid these results statistically, purely functional therapeutic effects of steroids in certain individual patients were still impressive. Since none of these drugs affected the disease fundamentally, the question was whether cortisone had not in some instances enabled the patient to "get more out of life," though happiness is not a scientific quality.[863] Steroids were still useful in certain patients in whom the disease remained active in spite of other therapy, including rest, salicylates and gold.[650, 735, 2675, 2676, 2677]

The use of corticotropin and cortisone today was compared with early opinions on the use of digitalis and ether.[1460] [Reports of indications, contraindications, complications and results of steroid therapy were too numerous to summarize in their entirety in this Review.—Ed.]

Indications for steroid therapy of rheumatoid arthritis varied. With minor variations, steroid therapy should be considered (1) for fulminant rheumatoid arthritis which does not respond to adequate conservative therapy, (2) for marked discomfort and pain which the patient could not reasonably be expected to bear, in spite of rest, corrective exercises, salicylates and constitutional therapy, (3) failure of gold salts after an adequate trial, and (4) as a temporary measure just before, during and after some orthopedic or rehabilitative procedure.[335, 1365] There were two important medical indications and a third social indication in patients (1) who developed progressive inanition and malnutrition as a result of the disease, in spite of six months or more of optimal conservative therapy, (2) with iritis whose vision was threatened, or who were about to undergo eye

surgery, and (3) who failed to improve significantly after three to six months' conservative therapy, and whose obligations required that they return to work, even at some future risk.[194] The aim of steroid therapy, according to Hench, was to provide optimal but not maximal relief, without the development of undesirable side-effects, and at a dosage governed by the patient's tolerance to steroids, rather than by the severity of his symptoms.[1402] [We agree.—Ed.]

Prednisone and Prednisolone. Prednisone (delta-1-cortisone) and prednisolone (delta-1-hydrocortisone) differ in chemical structure from cortisone and hydrocortisone, respectively, only in possession of a double bond between C-1 and C-2 in ring A. This modification of the molecule increased the antirheumatic potency by about four times, and decreased the electrolyte metabolic effect markedly, compared milligram for milligram with cortisone and hydrocortisone.[326, 440, 980, 2563, 2601, 3111, 3226] The pattern of clinical improvement after administration of prednisone and prednisolone, in 10 to 20 mg. daily dosage, corresponded closely to that of cortisone and hydrocortisone when used similarly in proportionately larger milligram doses.[324, 440, 1681, 2260, 3226]

The advantages of these two compounds were the considerable freedom from sodium and water retention, and the occasional anti-inflammatory response of certain individuals in whom cortisone no longer appeared to be effective. Patients with incipient or congestive heart failure, hypertension or edema tolerated them well.

The disadvantages were increased tendency to digestive disturbances and peptic ulcer, with its complications, and the questionably increased tendency to psychotic episodes.[324, 325, 440, 804, 956, 998, 1219, 1253, 1356, 2100, 2179, 2236, 2993] However, no increase in the incidence of peptic ulcers was reported.[604, 2677] Petechiae, purpura and ecchymoses were observed more often with prednisone than with cortisone therapy.[735, 753, 803, 2239] The incidence of osteoporosis of the spine was believed to be lower than with other corticosteroids; it was detected radiologically in only one of 23 patients after several months of treatment.[682] A group of elderly patients with various types of musculoskeletal conditions treated with prednisone in daily dosage of 3.0 to 6.0 mg. showed no sign of sodium retention.[2745] Administration of prednisone was associated in three patients with a rapid and marked depression of urinary excretion of 17-ketosteroids, a temporary negative nitrogen balance, increased sodium excretion, slight retention of potassium, rise in the serum cholesterol, rise in the serum albumin, and fall in the serum alpha and gamma globulins.[1149]

9 α-fluorohydrocortisone. Substitution of a fluorine atom at the C-9 position increased the antirheumatic potency of hydrocortisone and cortisone about 10 times, the anti-inflammatory effect seven times, and the glycogen-depositing effect about 13 times. But it also increased the sodium-retaining and potassium-losing effects about 50 times, so that this preparation could not be used effectively as an antirheumatic agent;[327, 365] the risk of hypokalemia was great when doses of more than 0.1 mg. were repeated.[1276] The addition of a double bond between carbon atoms 1 and 2 of 9 α-fluorohydrocortisone to form Δ-1, 9 α-fluorohydrocortisone resulted in about equal antirheumatic and anti-inflammatory effects, without decrease in the sodium-retaining or potassium-losing properties.[274, 1365] Thus, although it was 10 times more potent than prednisone in inhibiting corticotropin secretion and suppressing adrenal cortical function, it could not be used effectively in treatment of rheumatoid arthritis.[3174]

Triamcinolone. The addition of an hydroxyl group at the 16-carbon position eliminated the excessive electrolyte activity of 9 α-fluorination. Triamcinolone (9 α-fluoro-16 α-hydroxyprednisolone) contains a fluorine atom at the C-9 position and an hydroxyl group at the C-16 position. The antirheumatic effect was approximately four times that of hydrocortisone, and about the same as that of prednisolone, and there was no sodium retention; in several series of treated patients, edema formation, peptic ulcers, psychic irritation and hypertension were infrequent.[79, 1052, 1358, 1364, 1365, 3429] Facial rounding, purpura or ecchymoses, acne, increased sweating, and leg cramps, especially severe at night, were commonly observed side-effects.[1364, 1365] Other effects not common with other steroids included headache, dizziness, "light-headedness," sleepiness, erythema of face, neck, hands and forearms, easy fatigability, weakness and weight loss. Compression fractures occurred. Active peptic ulcer in 12 patients in whom triamcinolone was used to replace another steroid healed in seven on the usual ulcer management.[1052] [In long-term studies of adrenocortical steroids, it is at times difficult to separate the effects of prolonged administration of previously used steroids from the additive effects of the "newer" steroid.—Ed.] Sudden withdrawal of triamcinolone was attended by rapid re-accumulation of fluid in several patients.[2064] Fourteen patients previously on prednisone therapy for a variety of conditions were given triamcinolone; nine had no previous history of joint disease, but three of these developed an acute arthritis, which in two resembled rheumatoid arthritis.[3280] [The evidence for R.A. was not convincing.—Ed.]

Methylprednisolone. Addition of a methyl group at the C-6 position of prednisolone produced methylprednisolone, reported as little if at all more effective[323, 488, 2262, 2606] or slightly more potent than prednisolone; about two thirds of the milligram dosage of prednisolone gave an equivalent effect.[660] Side-effects were similar.[488, 2088, 2262, 2606] In doses of up to 5.0 mg. a day in normal healthy men, methylprednisolone had no effect on circulating eosinophils, or on nitrogen, carbohydrate or electrolyte metabolism. Doses as high as 100 mg. per day produced no sodium retention, but rather sodium diuresis.[1737] This preparation was an effective ACTH inhibitor, and its effect on carbohydrate tolerance was the same as that of prednisone and triamcinolone. A 15 to 20% increase in blood sugar was observed two hours after a glucose load administered after five or six days of therapy.[1783] In patients with R.A., methylprednisolone was as powerful as prednisolone in its nitrogen-wasting effect, and about as potent in its pituitary-adrenal function inhibition, circulating eosinophil-reducing effect, and sodium-retaining and potassium-losing activites.[223]

Dexamethasone. This analog of prednisone (delta-1, 9 α-fluoro, 16-α methyl hydrocortisone) had an antirheumatic effect greater, milligram for milligram, than any steroid so far used; potency was about six times that of prednisone, and 25 to 30 times that of hydrocortisone.[321, 327, 438, 2927] On a weight basis, its effect on suppression of corticotropin secretion by the pituitary was about 30 times greater than that of prednisone. In daily doses of 1 mg. to 4 mg. as used for therapy of R.A., no sodium retention, potassium loss or impairment of carbohydrate tolerance occurred. In larger, experimental doses of 6 to 10 mg. daily, no sodium retention or potassium loss was noted, but a negative nitrogen, calcium and phosphorus balance was produced.[438] [Severe muscular weakness associated with muscle atrophy may be a limiting factor in the quantity of 17-hydroxycorticosteroids which can be tolerated by certain patients. Two recent papers on steroid myopathy

are of considerable interest: (1) Perkoff, G. P., Silver, R., Tyler, F. H., Cartwright, G. E., and Wintrobe, W. W.: Am. J. Med. **26**: 891 (June) 1959; (2) MacLean, K., and Schur, P. H.: Lancet **1**: 701 (Apr. 4) 1959.—Ed.] [321, 327, 438, 2927] A striking decrease in eosinophils of the peripheral blood occurred within six hours of an oral dose.[2927] In 70 patients who had taken dexamethasone for three months or longer, upper gastrointestinal tract x-ray showed active peptic ulcers in six, five of them prepyloric. Four of these were asymptomatic, and one was mildly symptomatic; only one patient had typical ulcer symptoms; on strict ulcer management, five of the six healed within six weeks.[321]

Pattern of Clinical Effects. Clinical effects of cortisone, hydrocortisone and other like steroids were now well known; rapid suppression of pain and inflammation followed the administration of large doses. Smaller doses resulted in more gradual improvement but fewer side-effects early in the course of treatment.[650, 1462, 1465, 2675] Corticotropin was preferred over cortisone and like steroids for long-term therapy because atrophy of the adrenal cortex was avoided.[1600, 2676, 3290] [Even though adrenal cortical atrophy may be avoided, depression of pituitary function follows and is probably just as significant.—Ed.]

The only undesirable effects significantly altered by introduction of newer steroids were decrease in sodium retention and potassium loss which resulted from the use of delta-1 steroids, prednisone and prednisolone, or their derivatives. With increased antirheumatic potency of these substances, a comparable intensification of glucocorticoid and other effects occurred, and major hazards of steroid therapy remained.[260]

Pituitary-Adrenal Physiology. Cholesterol and acetate were generally accepted natural precursors of adrenocortical steroids.[787, 809] Use of C^{14}-labeled acetate revealed this substance to be a precursor of adrenal steroids. Conversion of C^{14} cholesterol was shown to be increased 18 times by the addition of ACTH, while conversion of another precursor, progesterone, to corticoid was increased only 17%. C^{14} acetate conversion to corticoid was increased only 14% by ACTH.[1554, 1555] It was also suggested that the influence of ACTH upon corticosteroid synthesis might be concerned with increasing the transfer of cholesterol through the mitochondrial membrane to make it available for the enzymatic apparatus.[1887] Specificity of ACTH resided not in control of specific tissue enzymes peculiar to the adrenal gland, as these enzymes were also present in the ovary, but in its specificity for adrenocortical tissue.[787]

The factor or factors capable of affecting the amount of adrenal secretion were unknown, but it was presumed that they were hormonal and were probably of pituitary origin.[1095, 1995, 2656] It was suggested that the action of corticotropin was to break down the side chain of cholesterol (C-27) to form a C-21 compound, or to build up acetate or similar C-2 substances into a C-21 steroid; the exact mechanism was not known.[3035]

Corticotropin, Adrenocorticotropin (ACTH). Corticotropin was a straight peptide chain of 39 amino acids.[780, 1887] But whether corticotropin was a "prohormone" converted to another form by enzymes was not yet known.[1887] On administration of ACTH, the healthy adrenal cortex increased its output of many of the 30 or more steroids produced by this organ.[3008] The level of circulating adrenal steroids, secretion of epinephrine and a neurohumeral mechanism were all involved in control of pituitary ACTH production,[1555] but cortisol was the only physiologically significant or naturally occurring suppressor of pituitary ACTH secretion in man.[787]

Repository preparations of ACTH intended for subcutaneous or intramuscular administration only were labeled according to subcutaneous USP units, while lyophilized corticotropins were quantitated as intravenous USP units. An intravenous USP

unit, the equivalent of an international unit, represented three or four times as much ACTH as did a USP subcutaneous unit. Commercial preparations, depending upon their purity, contained from one to 80 or more intravenous USP units per milligram of dry powder compared with a potency of 100 ± 20 units per milligram for pure ACTH. Maximal secretion resulted from one or more international units injected intravenously over an eight-hour period. The total secretory activity of the adrenal was proportional to duration rather than to intensity of stress.[780]

Under quiescent conditions the pituitary corticotropin output varied inversely with the concentration of cortisol in the blood. Overriding this basal "feedback" regulation was the stress reaction whereby additional corticotropin was released, probably in response to neurohormones from the hypothalamus, which reached the anterior pituitary by portal venous pathways.[1106]

The postoperative increase in 17-hydroxycorticoids associated with increased excretion of noradrenalin, and adrenalin, was evidence that the vegetative nervous system and the pituitary-adrenocortical system have a close relationship under stress.[1310] Capacity to suppress corticotropin secretion was common to all the glucocorticoids when given in amounts more than equivalent to the normal cortisol secretion of about 20 mg. per day.[1106]

Cortisol (Hydrocortisone). Hydrocortisone, or cortisol, the principal corticoid produced by the human adrenal cortex, was carried in the blood as free 17-hydroxycorticoid fraction loosely bound to protein. It left the blood stream at a remarkably constant rate in the presence of normal renal and liver function; with each circulation through the liver, as much as 30% was metabolized.[780] With trace quantities of intravenously administered hydrocortisone-4-C^{14}, the magnitude of the miscible pool of cortisol in the normal subject was 1.1 to 2.4 mg. Calculations of turnover rate of endogenously synthesized hydrocarbon ranged from 17 to 29 mg. per day in nine normal subjects. Following maximal stimulation with ACTH, the miscible pool of cortisol increased to 10 mg. and the turnover rate increased to 154 mg. per day in the normal subject. Both the miscible pool and the turnover rate of cortisol showed a diurnal variation.[2386]

Measurement of the 17-hydroxycorticosteroid (17-OHCS) level of serum following ACTH stimulation was the "best way" to measure adrenal cortical function; normal values varied from 3 to 26 μg. per 100 ml. This technic has allowed determination of steroid secretion with elimination of diurnal and day-to-day variations.[2307, 2657] [However, physiologically these may be very important.—Ed.] Free 17-hydroxycorticosteroids in the plasma of eight healthy children during six hours of intravenous ACTH infusion were highest from six to eight hours after start of the infusion and proved the procedure to be practical.[2307]

Free serum 17-hydroxycorticoids increased rapidly after a surgical operation: their fourfold increase in four hours exceeded the increase produced by maximal doses of ACTH over the same period. Measurement of free serum 17-hydroxycorticoids provided an index of timing intensity of adrenal response to injury. Urinary excretion of the total steroid furnished a better measurement of total duration and extent of this response.[2951] [But the time required to perform these tests precluded their usefulness as practical measures of the stress at the time adequate treatment is needed.—Ed.]

Excretion of steroids and metabolic products was mainly by glomerular filtration; 80% of administered hydrocortisone was excreted in the urine within the first 24 hours, and an additional 10% during the next 48 hours.[434] Conjugated metabolites appeared at a rate characterized by an exponential function with a half-excretion time of approximately four hours.[780] After oral or intravenous administration of hydrocortisone, labeled steroid metabolites appeared in the urine in the same quantities and at similar rates.[1400] Measurement in urine of conjugated 17-hydroxycorticosteroids reflected, at least roughly, the adrenal output of cortisol if no serious renal or hepatic disease was present.[3288]

Diurnal rhythm in the levels of plasma 17-hydroxycorticosteroids, with a low value at midnight and a high maximum from 5:00 to 8:00 a.m., usually near 6:00 a.m., was observed; 17-hydroxysteroid excretion in urine followed the same general curve but was delayed about two hours. Night workers and blind persons had identical diurnal and early morning variation which was not related to sleeping.[2138] Urinary sodium excretion was not closely correlated with 17-hydroxycorticoid excretion, but followed the same trend as potassium excretion when group figures were used.[789]

Cortisone. Administered cortisone was metabolized to hydrocortisone very rapidly. Infusion of tracer quantities of cortisone-4-C^{14} showed the biologic half-life of the unconjugated radioactive metabolites to be 35 to 55 minutes. Absorption from the gastrointestinal tract was rapid and complete. Most or all of the biologic activity of cortisone could be accounted for by the fraction transformed to hydrocortisone. Approximately 90% of administered cortisone was excreted as urinary metabolites in 72 hours, shown by excretion of C^{14} following infusion of labeled steroid.[2387] Dialysis equilibrium experiments on human plasma obtained two hours after ingestion of oral cortisone acetate showed an average of 94% of 17-hydroxycorticosteroids and 65% of 17-hydroxycorticosteroid glucuronides loosely bound to plasma proteins.[725]

Hydrocortisone-4-C^{14} was shown by electrophoretic migration to be bound to the albumin component of normal plasma. Affinity of hydrocortisone-4-C^{14} was greatest for normal human albumin (Fraction V) and least for bovine plasma albumin.[726] The binding of cortisol by plasma at high concentrations of hormone was attributed to albumin.[727] With different methods, lower values for steroid-albumin binding were found. Interaction between low concentrations of cortisol-4-C^{14} or progesterone-4-C^{14} and serum proteins was studied by paper electrophoretic methods in human serum albumin solution and in human and rat serum. Between 2 and 10% of cortisol and between 70 and 90% of progesterone were found to be bound and thus transported by albumin.[3292] [These studies were really not comparable.—Ed.]

Delta-1-hydrocortisone. Oral or intravenous administration of delta-1-hydrocortisone (prednisolone) resulted in greater and more lasting plasma elevation of 17-hydroxycorticosteroids than did hydrocortisone. The mean half-life of intravenously administered prednisolone obtained in eight subjects was 192 minutes—again, longer than that of intravenous hydrocortisone, which varied from 90 to 115 minutes. The slower metabolism of the delta-1-form contributed to its greater clinical effectiveness.[908] In the dog, Δ 1-cortisol was first converted to cortisol by reduction of the C-1 double bond before further saturation of the ring A at C-4 and further hydrolysis of the C-2 ketone.[1738] [This was not true in the human.—Ed.]

The 1-17-hydroxycorticosteroids from prednisone and prednisolone, unlike the 17-hydroxycorticosteroids from cortisone and hydrocortisone, were not appreciably converted to 17-ketosteroids, and actually suppressed urinary 17-ketosteroid excretion.[2844]

The metabolic effects of 6-methylprednisone and prednisolone in normals were similar. The 6-methyl derivative in some subjects caused increases in sodium excretion and total urinary nitrogen output. During six-hour intravenous infusions, neither produced a change in inulin or p-aminohippurate clearances, but potassium clearances rose. The half-time of 6-methyl-prednisolone in venous blood was only slightly greater than that of prednisolone, but both were removed from the circulation at a significantly slower rate than was hydrocortisone.[1569]

The biologic half-time (i.e., the time required for one-half of an intravenously administered dose to disappear from the plasma) of dexamethasone in normal subjects was 170 to 210 minutes, that for hydrocortisone, 95 to 120 minutues, and for prednisolone, about 200 minutes. The capacity of dexamethasone to suppress corticotropin production was 30 times greater than that of prednisone. Dexamethasone also produced a significant and sustained negative calcium balance, chiefly and uniquely a result of increased fecal excretion.[438]

Mode of Action. The pharmacologic potency of any corticoid depended upon the responsiveness of the end organ. Also, potency of a given corticoid was defined in terms of "intensity" factor and "time or duration" factor. The unsaturated delta-1-derivatives of hydrocortisone or cortisone (prednisolone or prednisone) derived some of their relatively increased anti-inflammatory potency from a longer half-life as an active corticoid in the plasma.[780]

Little was known of the exact mechanism of action of corticoids within cells, though a number of enzyme systems were affected.[2221] Biochemically, corticosteroids influenced the metabolism of protein, fat, carbohydrate, purines, electrolytes and water, and exerted a direct calorigenic action.[1106] These effects were mediated by corticoids having, in common with other biologically active steroids secreted by the adrenal cortex, a 21 carbon chain, the unsaturation of ring A and oxygen substitutions in positions 3, 20 and 21. Moreover, the most specific structural requirements relating to intermediary metabolic activity of naturally occurring steroids appeared to be the oxygen substitutions in positions 11 and 17.[3095]

The ability of rheumatoid synovial tissue to metabolize hydrocortisone and cortisone *in vivo* was confirmed by finding several metabolites following injections of hydrocortisone and cortisone into the knee joint. Substantial amounts of hydrocortisone were found after the injection of cortisone. Patterns of metabolites of the two were entirely different. When extracted synovial fluid was incubated, first with B-glucuronidase and then with papain, and each incubation followed by solvent extraction, further yields of steroids were obtained.[3326]

Therapeutic Results. Similar clinical effects were obtained in patients with R.A. treated with equivalent doses of corticotropin, cortisone, hydrocortisone, prednisone, prednisolone, 9-α-fluorocortisone, triamcinolone, methylprednisolone or dexamethasone.[194, 275, 321, 326, 327, 438, 604, 804, 956, 980, 998, 1052, 1356, 1358, 1365, 1486, 2100, 2563, 2606, 2993, 3429] The mineralocorticoid effect varied; newer steroids in general had less sodium-retaining effect, and edema was much less frequent.[194, 275, 324, 326, 956, 1052, 1356, 2260, 2563] Subjective and objective improvement was accompanied by reduction in erythrocyte sedimentation rate, disappearance of C-reactive protein, eosinopenia, increased serum albumin, increased hematocrit and hemoglobin concentration, and reduction of the inflammatory reaction of synovial membrane of affected joints. Rate of improvement often diminished when therapy continued for long periods, but increased functional capacity remained.[275, 804] Various series of steroid-treated patients, ranging from eight to 156, were reported,[194, 275, 326, 327, 391, 956, 980, 998, 1052, 1460, 1600, 1681, 2100, 2260, 2292, 2563, 2993] but it was difficult to do controlled studies. Varying degrees of improvement were observed in 36 of a group of 50 treated patients; 27 were receiving cortisone or other steroids at the time of the report. Cortisone had been discontinued in 23 individuals because of inadequate response in 12 cases, death in five instances (attributed in part to cortisone in two), remission of disease in four patients (three of these children), and request of the patient in two instances. Serious complications totaled 18: duodenal ulcer, five; serious infections, five; congestive heart failure, three; diabetes mellitus, two; compression fracture of the spine, two; and malignant hypertension, one. However, in only three cases was cortisone discontinued because of toxic effects.[194]

Of 148 patients treated with cortisone for from one to three years, two thirds were over age 50, and 76% were in stages III and IV. Initial improvement occurred in 74%; in about one third, treatment had to be discontinued because of side-effects. Only six patients had remissions, and 15 died. Side-effects were

particularly frequent in advanced cases and older patients. One third had no side-effects, and in another third, treatment was carried through in spite of moderate side effects.[2292]

Of 68 patients treated with cortisone or ACTH for periods ranging from six months to five and one-half years, 60 exhibited advanced arthritic lesions by x-ray (stages III and IV by the ARA classification).[1486] In order to reduce complications, the hormone dosage was held at levels which gave only suboptimal relief of symptoms. Steroid therapy was discontinued in five patients because of remissions, and in 27 because of complications; eleven of the 27 died. Of 12 patients living from two to three years after discontinuance of steroid therapy, 11 were chair- or bed-ridden with continuing manifestations of active rheumatoid disease. At the termination of the study, 36 patients were still on steroid therapy and continued to manifest physical signs and laboratory evidences of rheumatoid activity; the majority showed x-ray evidence of progressive joint destruction. Untoward events tended to occur in patients with associated disease and debilitation.[1486] Effects of cortisone were no different in 13 children with juvenile rheumatoid arthritis from those in adults with the disease; progression continued in several, and results were similar to those in 12 treated with aspirin.[90] Of 167 patients, 47 were given prednisone because of failure to improve on other treatment; improvement in functional capacity occurred in 50%, and subjective improvement in 90%.[956] In 156 patients, side-effects from prednisone were not particularly disturbing, though peptic ulcer was noted in seven of 43 with dyspepsia.[2993] Prednisone was effective in suppressing manifestations of Still's disease.[1766]

In a study of 67 patients with R.A., triamcinolone suppressed rheumatic manifestations in doses roughly proportional to those of prednisone and prenisolone. Side-effects were slower in appearing, but triamcinolone produced several, particularly the masculinizing effect, cutaneous purpura or ecchymosis, increased sweating, and leg cramps.[1365] The dose ratio of triamcinolone to prednisolone was four to five;[1358, 3429] in 74 patients given triamcinolone, the over-all requirement in milligrams was about 90% of that of prednisone.[1052]

Preliminary studies with methylprednisolone showed it to possess approximately the same antirheumatic potency as prednisone in 41[323] and in 20 patients;[2262] it was about 25% more effective, milligram for milligram, than was prednisolone,[260] but evidence of any superiority was not convincing.[323, 2262, 2606] Dexamethasone was about six or seven times more potent, milligram for milligram, than was prednisolone.[327, 438]

The patient's functional capacity was an index of subjective response to treatment, hard to evaluate quantitatively, but in most cases greater than objective improvement.[956, 1486] Improvement with steroid therapy was most marked in the first three months, and thereafter often decreased gradually as the disease progressed.[2179] Progression of the disease was shown by development of physical deformities, such as ulnar deviation of fingers, subluxations and contractures, subcutaneous nodules, joint effusions, pericarditis or pleuritis. X-ray findings showed new punched-out areas or cysts in bone, narrowed joint spaces, and ankyloses developing even while patients were on steroid therapy and apparently "doing well." Remissions of rheumatoid arthritis during steroid therapy were rare in the severely afflicted, though partial and temporary remissions occurred.[1486]

Effects on Laboratory and Pathologic Manifestations

Erythrocyte sedimentation rate, plasma fibrinogen, C-reactive protein, serum hexosamine, serum mucoprotein and total serum polysaccharides were consistently reduced toward normal in rheumatoid arthritics treated adequately with cortisone or hydrocortisone. Their mucoprotein and hexosamine values were not affected by evanescent fluctuations in disease activity, and seldom reached normal.[1159] There was general agreement on the eosinopenia and increased 17-hydroxycorticoid urinary excretion associated with adequate doses of steroid therapy. No consistent changes in uric acid values were noted.[2601]

Adrenocortical capacity tests, utilizing six-hour intravenous ACTH stimulation and measurement of plasma 17-OHCS levels, were a highly sensitive index of adrenocortical activity, and were applicable to routine clinical use. Plasma 17-OHCS levels and adrenocortical capacity were greatly reduced in most patients on long-term cortisol or cortisone therapy. The adrenal cortex in some patients showed a remarkable return to normal function after abrupt cessation of steroid therapy.[2658] Triamcinolone depressed urinary 17-ketosteroid excretion.[2064]

In over 100 cases of rheumatoid arthritis the total 17-ketosteroid excretion was in the lower range of normal, and the mean urinary excretion of 17-hydroxycorticosteroids in 20 patients with R.A. was about 50% below normal. 17-α-hydroxypregnanolone was present in equally large amounts in the urine of both normal subjects and those with R.A. There was a percentage increase in excretion of ketonic corticosteroids. In pregnancy the 17-ketosteroid pattern showed a fall of androsterone and etiocholanolone, and a rise in 11-oxy-17-ketosteroids; a similar pattern was observed after sufficiently large doses of cortisone. Since other 17-ketosteroids were not increased, the placenta rather than the female adrenals was considered to be the steroid source. That excretion of 17-ketosteroids and corticosteroids was reduced in hepatitis suggested that this disease affected rheumatoid arthritis through disturbed steroid metabolism rather than by increased steroid production.[263, 265]

An increase of 123 to 178 mg./100 ml. in protein-bound hexose was demonstrated in 20 patients with R.A. A decrease in serum sulfhydryl was demonstrated, ranging from 0.062 mM sulfhydryl per 100 ml. serum in 10 normals, to 0.039 mM sulfhydryl in 10 patients with R.A.; decrease in available sulfhydryl groups modified cellular activity and probably protein synthesis with a greater glycoprotein formation. [Others have attributed this to increased tissue breakdown.—Ed.] Decrease in serum glycoprotein was demonstrated during therapy with adrenocortical steroids conducted on five patients; in three of these, low pretreatment values for serum sulfhydryl were elevated during therapy.[1821]

Metabolic effects of prednisone were followed in three women with R.A. Nitrogen balance first became negative but, with improved appetite, became positive. Sodium excretion increased, and the concentration of cholesterol in the serum rose significantly. The abnormal serum protein pattern of R.A. was normalized, with depression of the alpha and gamma globulins and a rise in albumin concentration.[1149] Species characteristics and interspecies differences in response patterns of serum components to cortisone made correlation of metabolic studies in man and animals very difficult. After cortisone administration, humans had hypoalbuminemia and increased levels of gamma and beta globulins, as well as of the 0-fraction of the lipoproteins, and of serum lipids.[349]

Pathology

Pathologic changes in the pituitary glands of patients who had received massive steroid dosage correlated poorly with the changes in pituitary glands of patients receiving low maintenance dosage of steroids.[670] Postmortem examination of the pituitary glands of 76 patients who had received varying amounts of cortisone, ACTH or both prior to death from various unrelated diseases showed changes in the basophil cells. The finding of completely hyalinized basophils almost indistinguishable from Crooke cells was considered to be evidence that the Crooke cell was secondary to and not the cause of Cushing's syndrome.[1715]

The anti-inflammatory action of cortisone upon the acute cellular response to thermal injury was studied in the rabbit ear chamber. The hormone suppressed the reaction of acute inflammation in the earliest recognizable phase, that involving vasodilatation and adherence of leukocytes to the vascular endothelium. The anti-inflammatory effect was on the basis of its vasoconstrictive properties alone. The findings supported the hypothesis that cortisone exerted a direct protective action upon the endothelial cells and leukocytes, and rendered them refractory to the tissue products which initiate inflammation.[3360]

The effect of cortisone on the cellular response to an intraperitoneal injection of pollen into pollen-sensitized mice was studied. Subcutaneous injections of cortisone acetate caused a prolonged decrease in the number of blood lymphocytes and a temporary decrease in monocytes. The accumulation of mononuclear cells at the site of the challenging antigen injection was completely inhibited. Eosinophils were decreased in number in both the blood and the peritoneal fluid. A close relationship between the accumulation of eosinophils and immune reactions was observed. The presence of these cells around foreign materials was correlated with active antibody formation, but not with local antigen-antibody reactions, shock or nonspecific protein breakdown.[2923]

Comparative Effects of Steroids. Comparative antirheumatic effects of steroids were fairly well established. Equivalent full suppressive doses of cortisone, hydrocortisone, prednisone and prednisolone were 100 mg., 80 mg., 20 mg. and 20 mg., respectively, when given in four divided doses every six hours;[3226] thus, prednisone was about five times as potent as cortisone.[980] Triamcinolone and methylprednisolone were very slightly more potent, milligram for milligram, than was prednisone or prednisolone.[260, 1365] The antirheumatic effect of dexamethasone was about six times that of prednisolone, and its corticotropin inhibitory effect was about 30 times greater than that of prednisone.[438] [The full suppressive doses of triamcinolone and methylprednisolone have been found to be 16 mg. daily given in four divided doses of 4 mg. each, and of dexamethasone, 3 mg. daily given in four divided doses of 0.75 mg. every six hours.—Ed.]

Prednisolone suppressed many of the changes of R.A. in 28 patients more than four times as effectively as hydrocortisone, milligram for milligram.[2563] Prednisone in daily doses of 15 or 20 mg. was as effective in 38 patients as were four or five times that amount in milligrams of cortisone.[1681] Thirty-five of 68 patients with R.A. who had been taking cortisone for a year were transferred to prednisone therapy; the remainder continued to take cortisone. After another year of therapy, those on cortisone showed little change, while the prednisone group showed some improvement, especially marked during the first few months; in some cases the dosage was reduced to decrease the chance of side-effects.

Even so, side-effects were noted in a higher percentage of the prednisone group than of the cortisone group.[2100] [The average daily dose of cortisone, 60 mg., was proportionately smaller than the 14 mg. to 20 mg. daily doses of prednisone used.—Ed.] Although assessment of 25 patients with long-standing, severe R.A. at the twelfth and twenty-fourth weeks of steroid therapy suggested that the prednisolone group fared slightly better than those on hydrocortisone, results did not justify prolonged prednisolone therapy.[998]

As practical therapeutic agents, prednisone and prednisolone shared most of the shortcomings of other steroids. Compared with hydrocortisone, they had the advantage of relatively little salt and water retention, and the disadvantage of more frequent digestive tract complications.[326] A comparison of triamcinolone and prednisone with dosage ratio of 4 : 5 showed little difference in patient's preference or objective results.[1365]

Corticotropin. Potency of corticotropin varied widely.[73, 780, 1116, 1161, 2676, 3008, 3287] Pure corticotropin had a potency of 100 ± 20 USP units per milligram. Commercial preparations varied from 1 to 80 or more intravenous units per milligram of dry powder.[780] Plasma level determinations of 17-hydroxycorticosteroids were elevated in non-endocrine diseases following administration of repository corticotropin; this measure of adrenal cortical activity was superior to the measure of 24-hour urinary 17-hydroxycorticosteroid excretion.[1116] However, urinary excretion was still a reliable method of evaluating response of the adrenal cortex to corticotropin.[780, 3287] Maximal stimulation of the adrenal was accomplished by small amounts of corticotropin. Total secretory activity was proportional to duration rather than to intensity of stress.[780] Eosinophil counts and excretion of 17-ketosteroids were not accurate measures of adrenocortical activity.[3287] Treatment with corticotropin was adjusted on the basis of clinical response and of frequent, often weekly determination of urinary 17-hydroxycorticosteroids;[2676, 3287] a dose adequate to maintain an output of 20 to 35 mg. of 17-hydroxycorticosteroids, double the normal output, was given. [This dosage varied greatly, depending upon the preparation used.—Ed.] Roentgenographic bone changes were less often reported after corticotropin therapy than after steroid treatment. Disadvantages of corticotropin therapy included variation in response, acquired resistance, and the usual side-effects.[73, 2676, 3287, 3289] In 20 of 66 patients, corticotropin was discontinued because of acquired resistance, and in 16 others because of hypertension, edema or heart failure.[73]

Of 45 patients with R.A. and three with rheumatoid (ankylosing) spondylitis given ACTH, a satisfactory result was observed after six months in 73%, and after 12 months in 56%; secondary effects were of the same kind and degree as those produced by cortisone. However, ACTH was preferable for long-term treatment, to avoid atrophy of the adrenal cortex, while cortisone was preferable for "acute situations," where the adrenal gland was "already markedly stimulated."[1600] [This fails to consider the hyporesponsiveness of the pituitary gland in patients receiving corticotropin.—Ed.]

Combined Steroid and Corticotropin Therapy. Adrenocortical steroids depressed adrenocortical function, but atrophy of the adrenal cortex was reversible. The low 17-hydroxycorticosteroid urinary excretion which followed ACTH stimulation after withdrawal of steroids demonstrated this depressed function.[1773, 3171, 3289] Termination of steroid therapy with a week of combined corticotropin and steroid administration, followed by a few days of corticotropin therapy alone,

accelerated the return of normal adrenal cortical function. Pituitary hyporesponsiveness undoubtedly occurred, but definite tests for it were not available.[3171] A "normal adrenocortical capacity" developed from seven to nine days after withdrawal of steroid therapy in those patients given intramuscular repository ACTH during this interval. Of those not receiving repository ACTH, only one of five responded normally as much as 30 days later.[1773] Concurrent administration of 200 units or more of a long-acting repository corticotropin at weekly intervals usually prevented development of adrenal cortical unresponsiveness to corticotropin, as measured by the total 24-hour urinary excretion of 17-hydroxycorticosteroids, but repository corticotropin at weekly intervals did not restore lost adrenal cortical responsiveness.[2480] Intermittent administration of corticotropin during steroid therapy was advised,[264, 2480] but its effect on the hypophysis remained an open question.[3162] Although ACTH might prevent atrophy of the adrenal cortex, it did not solve the problem of relative adrenocortical insufficiency which, for a time after adrenocorticosteroid therapy, left the patient vulnerable to the stress of infection, surgery or trauma.[2977] [This period of relative vulnerability needs more emphasis.—Ed.]

Attempts to Potentiate Adrenocortical Steroids. Some form of salicylate, usually aspirin, was generally used as an adjunct to steroid therapy, but there was no advantage in combining different salicylates with small amounts of steroid in a single tablet.[2480] This practice was objectionable because it distorted the safety of steroid administration and restricted flexibility of dosage of the separate ingredients for the individual needs of the patient.[434] [There is no acceptable basis for use of the multitude of "steroid-combination" tablets commercially available.—Ed.]

Effects of salicylates were not mediated by way of the pituitary gland or adrenal cortex,[1415, 2385, 3096] though it was suggested that salicylates increased endogenous cortisone excretion.[1415] Administration of salicylates to normal subjects and to patients with R.A. did not alter the plasma concentration of hydrocortisone or corticosterone or urinary excretion of 17-ketosteroids. Three subjects given large doses of salicylates for 30 or more days had significant decreases in the urine corticoid concentration, and in rate of metabolism and rate of synthesis of hydrocortisone, but moderate doses for a few days produced no such changes. Salicylates evoked a satisfactory antirheumatic response in a patient with R.A. whose adrenal function had been markedly or completely suppressed.[959]

Steroid compounds with tranquilizing drugs were recommended for patients with R.A. who were nervous, depressed, anxious and insomniac;[2480] in 12 of 21 patients,[3230] and in 12 of 24,[3106] the maintenance dose of prednisolone was reduced substantially when hydroxyzine was also given. Clinical improvement, reduction of steroid dosage, or both, were achieved in 18 of the 21. In most patients, tranquilizing effect was not accompanied by drowsiness.[3230]

Isonicotinic acid hydrazide (INH) inhibited the inactivation of cortisone by liver slices and the hydroxylation of the conjugated unsaturated system of the cortisone molecule, but did not protect the side chain. This suggested that INH might potentiate the action of cortisone *in vivo* by retarding liver inactivation.[3300] In 39 patients with R.A., 400 mg. of INH and 37.5 mg. cortisone controlled arthritic manifestations; the withdrawal of either resulted in development of joint manifestations.[3301] [This needs to be confirmed. INH has a significant toxicity which warrants special care whenever this drug is used.—Ed.] Gold and phenylbutazone failed to modify detectably the response to or dosage of steroids needed, except in two of 22 patients given phenylbutazone, and one of six patients given adequate gold therapy.[1486]

Methods of Administration. Rapid and complete absorption of steroids of the cortisol type from the gastrointestinal tract simplified their administration. However, the daily dosage had to be divided, as any one dose was effective for only eight hours or less. In an emergency, cortisol was best administered intravenously, and cortisone or related steroids intramuscularly.[1402]

Oral Administration. The use of large suppressive doses at the start of treatment had chiefly given way to beginning with the estimated maintenance dosage of the chosen steroid.[795, 1460, 1465, 2675] In general, the dosages of steroids now used for chronic R.A. are smaller than formerly. Only reversible tissue reactions were favorably affected; attempts to modify irreversible changes led to trouble.[2416] Determination of dosage needed for a reasonable effect required skill on the part of the physician. Since symptoms varied from hour to hour and from day to day, a smaller fraction of the day's total dosage, and decreased dosages on days when patients were having less pain, could be used to keep the total daily dosage lower and to provide smoother, more even control of symptoms, without development of hypercortisonism[1402] [or at least a lessened chance of hypercortisonism.—Ed.]. "Dose tailoring," a term proposed by Hench, required the physician's attention and time, and an intelligent and coöperative patient. Dose reductions were begun as soon as the effect of the initial dosage had been evaluated; decrements or increments were small. Aspirin or other analgesics, heat application and additional rest would often prove more effective than an increase in steroid dosage. Patients had to be taught to accept a less than maximal effect from steroids.[434, 795, 1161, 1402, 2416, 3226]

The long-term use of steroids in "full doses" in patients with R.A. was not tolerated indefinitely. Postmenopausal women usually tolerated well a total daily dosage of 20 to 30 mg. of cortisone or its equivalent in other steroids. For premenopausal women, 30 to 37.5 mg. cortisone, and for adult men, 37.5 to 50 mg. cortisone, were maximal, if hypercortisonism was to be avoided.[1465, 2416] [These dosages are lower than most patients or some physicians willingly accept. However, an effort to carry patients at such dose levels will reduce the number of complications and result in better tolerated long-term therapy. It may be impossible in many instances to reduce the daily dosage to these recommended values, but for patients being newly started on steroids, tolerance is more satisfactory. Occasionally some patients may tolerate doses somewhat in excess of these average values.—Ed.]

Up to 30 mg. of hydrocortisone or its equivalent in another steroid could be given daily in a single dose between 8:00 and 10:00 a.m., when spontaneous activity of the adrenal cortex was minimal, without seriously suppressing endogenous adrenal secretory activity.[780] [This has not proved to be a satisfactory alternative steroid program, however.—Ed.]

"Acute phase" tests, including erythrocyte sedimentation rate, plasma fibrinogen, C-reacting protein, serum hexosamine, serum (Winzler) mucoprotein, total serum polysaccharide and the resordin test, were not reliable enough in individual cases to be recommended as clinical aids to "dose tailoring." Possibly mucoprotein and hexosamine values could be used to distinguish between a true remission and therapeutic suppression of signs and symptoms.[1159]

Intravenous and Parenteral Steroids. Administration of hydrocortisone-free alcohol during emergencies proved to be of great value. It was rapidly eliminated, and intramuscular injections of cortisone were advised when intravenous administration was discontinued.[2924] Hydrocortisone was the most frequently

used adrenocortical steroid for intravenous administration. Prednisolone acetate was given as a weekly depot injection for periods of from 16 to 45 weeks to 16 patients with severe R.A.; gastrointestinal disturbances were less frequent than with oral administration.

Corticotropin. More effective long-term therapy with corticotropin was accomplished with delayed absorption preparations, corticotropin in gelatin (Gel-ACTH) and corticotropin-zinc oxide (Zinc-ACTH).[152, 2677, 3008, 3289, 3290] Standardization of long-acting preparations of corticotropin was possible by measurement of plasma steroid levels at specified times after administration of repository corticotropin to human subjects. Zinc-ACTH was effective for a longer period than was Gel-ACTH. Plasma levels of 17-hydroxycorticosteroids were significantly elevated in all of 11 non-endocrine patients two hours after the intramuscular injection of 20 to 40 units of Zinc-ACTH, and remained high in eight of 10 patients in whom eight-hour determinations were made. In six patients given 40 units of Gel-ACTH intramuscularly, peak response of 17-hydroxycorticosteroids at the end of two hours was followed in all instances by return to control levels at eight hours.[1116] Action of corticotropin zinc hydroxide as determined clinically lasted from one to seven days. For equal symptomatic suppression, zinc corticotropin was used in doses two thirds of that required by corticotropin in gelatin.[152]

Intramuscular injection of highly purified corticotropin, continued for prolonged periods in 51 patients, resulted in acquired resistance to one or more preparations of corticotropin by 42 patients. Cell-fixed antibodies were probably the main cause of acquired resistance. That preparations were allergenic was shown by allergic reactions at the site of injection in 17 patients. The allergenic nature of the corticotropin was attributed to the contaminating or "carrier" protein.[3287, 3290]

Intra-articular Steroids. In a high percentage of those patients with only one or two affected joints, the intra-articular injection of hydrocortisone or several of its esters was again found effective in allaying local manifestations.[650, 673, 831, 1162, 1460, 1690, 2282, 2383, 2644, 2678, 3371, 3426, 3427] Rigidly aseptic technic was essential to avoid infection.[627, 831, 1460, 3242] Ideal sites for paracentesis, use of positioning to aid palpation and to stretch the joint capsule and enlarge the target area, and avoidance of scoring cartilage were discussed.[2154, 2155]

A hypospray jet injector was used for intra-articular injection; on the basis of recovery of trypan blue and hydrocortisone acetate, a significant portion of the injected material reached the joint cavity, and no serious complications resulted.[3420] Hydrocortisone tertiary butylacetate was a less soluble higher ester, less readily absorbed and with a more prolonged local action. The injected substances disappeared from the joint fluid, but some hydrocortisone was retained by synovial cells.[627, 1162] Good results were reported from the intra-articular injection of hyaluronidase, 1,000 units, combined with hydrocortisone.[1690] The optimal dose of hydrocortisone acetate or hydrocortisone tertiary butylacetate (TBA) was 25 to 37.5 mg., even for large joints.[532, 1460, 3426] Prednisolone butylacetate was also used, in 20 to 30 mg. amounts, for large joints, and in 7.5 to 10 mg. amounts for small joints.[661, 1689] Improvement in the treated joint lasted for from two to three weeks.[3426] Clinically[673, 3426] and statistically,[532] differences in effects of hydrocortisone and hydrocortisone-TBA were present[2282] but not significant. However, in 24 patients with R.A., both drugs showed

advantages over a placebo.[532] The apparent slight advantage of hydrocortisone acetate over procaine was not statistically significant.[953] Severe pain shortly after intra-articular injection of any steroid, or four to six hours later, was not uncommon.[661, 2383] A small quantity of 1% procaine hydrochloride mixed with steroid prior to injection made the procedure less painful.[627]

Hydrocortisone acetate in greater concentrations than were usually used (up to 250 mg. per milliliter) produced relief in a greater number of patients, and to a greater degree than did injections of 25 to 50 mg. of the same preparation.[634, 2282] Duration of improvement increased from six to 34 days. That hydrocortisone was absorbed from the joints was shown by improvement of the uninjected joints of many patients receiving large amounts. Ninety per cent of those with evidence of a systemic effect had received 50 mg. or more of the steroid intra-articularly.[2282]

It was reported that intra-articular prednisolone acetate injected into joints of six hydrocortisone-resistant patients gave a longer period of relief, a lower incidence of local reaction and a slightly more rapid onset of effect in the acutely inflamed injected rheumatoid arthritic joint.[1689] No significant difference in response to 790 intra-articular injections of hydrocortisone acetate, hydrocortisone-TBA, prednisone acetate and prednisolone acetate in 80 patients could be demonstrated when 25-mg. doses were compared. Dosages were varied from 5 to 100 mg., and the larger and smaller doses produced the same improvement as the 25-mg. doses. About 75% of R.A. joints showed satisfactory improvement.[3427] Intra-articular injection of prednisone acetate was clinically beneficial, at least for a time, in 80 to 85% of joints.[831, 2383, 2678, 3426] Of more than 1,000 injections of hydrocortisone into 105 joints of 60 patients with R.A., favorable response was not achieved in 19% of the joints. Some degree of help was obtained in 31%; in the remaining 50%, worth while and sustained results were obtained with serial injections.[831] Good results were obtained in 29 of 37 proximal interphalangeal joints, and in nine of 10 metacarpophalangeal joints injected with hydrocortisone acetate.[3371] One hundred thirty-three R.A. patients treated with intra-articular injections of hydrocortisone obtained good results only in the finger joints.[2644]

There was a fairly satisfactory correlation between viscosity increase and the cell number decrease in joint fluid, and in symptomatic and objective response to intra-articular injections of hydrocortisone.[831] The relative electrophoretic mobilities of R.A. synovial fluid proteins approached those of normal fluid, but reversion was not complete. The absolute mobility of hyaluronic acid did not change significantly with clinical improvement, but that of some of the protein components did change.[2403] After intra-articular injection of hydrocortisone acetate, the synovial fluids of 34 R.A. patients showed average sodium ion concentration, originally close to serum values, to be decreased toward normal. Average protein and potassium values remained unchanged, and viscosity increased.[3383]

Hydrocortisone acetate intra-articularly rendered the precipitated polysaccharide derived from the synovial fluid less soluble in the presence of sodium chloride. The ratio of glucosamine/uronic acid in this complex had apparently increased.[1621] Extracted synovial fluid treated with enzymes and again extracted yielded more steroids, indicating that they were bound to the protein of synovial fluid by linkages which involved intact protein structure and which were not available in peptides of amino acids.[942, 3326]

Human serum albumin labeled with I^{131} disappeared faster from knee joints containing exudates or with thickened capsules than from clinically normal knees. Intra-articular injection of hydrocortisone acetate into the affected joints retarded or normalized the disappearance rate or absorption of the I^{131}.[24] Intra-articularly injected hydrocortisone, cortisone or their acetates disappeared rapidly from the joint cavity, about 85 and 98% after one and three hours, respectively, explaining the systemic hormonal effects that followed intra-articular steroid injection. Hydrocortisone acetate was absorbed from the joint more slowly than when it was administered orally, probably because a portion accumulated and was activated in the synovial tissue. Failure to demonstrate significant quantities of conjugated plasma 17-hydroxycorticosteroids after intra-articular injection of prednisolone acetate showed that prednisolone acetate absorbed into the blood remained unmetabolized and free, in accordance with the known fact that prednisolone 17-hydroxycorticosteroids were excreted in the urine unconjugated and for the most part unchanged.[2305]

Radiologic deterioration was observed in 13 of 25 knees treated with local injections of hydrocortisone, despite significant clinical improvement, and was attributed to tolerance for more weight-bearing function than might otherwise have been accomplished; a virtual Charcot's arthropathy sometimes occurred.[531] [This may occur in patients treated systemically with oral steroids also.—Ed.]

Other untoward effects following local hydrocortisone injection included generalized urticaria, bronchospasm, purpura, gastrointestinal bleeding, nausea and vertigo, localized urticaria and local weakness, infection and flare-up of symptoms.[1691] [These effects are not attributable to the steroid dosage generally used. —Ed.]

Complications of Hormone Therapy. Frequency and severity of complications correlated well with dosage, duration of therapy and severity of the rheumatoid process.[326, 434, 795, 1486]

Side-effects were more common in women than in men, and more frequent during or after the menopause.[2675] In 68 patients with R.A. given corticosteroids for five years, 41 different untoward effects were observed; the aggregate number for the 68 patients was 404. Most effects were minor, but in 27 patients steroids were discontinued because of severe complications, and 11 of this group died. Causes of death or major contributing factors included "malignant" R.A. in two patients, and each of the following in one patient: pneumonia, bleeding duodenal ulcer, bleeding gastric ulcer and amyloidosis, perforated duodenal ulcer, uremia secondary to pyelonephritis, parotid carcinoma and cardiac failure, acute bacterial endocarditis and apoplexy. Cause of death was undetermined in one instance. Reasons for discontinuation of corticosteroid therapy were (1) serious associated disease, (2) severe debilitation, and (3) higher steroid dosage needed to maintain suboptimal control.[1486] Cortisone was discontinued in 23 of 50 R.A. patients, 18 of whom had developed a serious complication; however, steroids had to be discontinued in only three. The most common cause for discontinuance was inadequate response.[194]

Untoward effects or side-effects included obesity, moon-face, "buffalo hump," enlarged supraclavicular fat pads, hirsutism, acne, striae, distention of the abdomen, atrophy of muscles of the extremities, insomnia, depression, osteoporosis, edema, menstrual disturbances, hypertension, thrombophlebitis, glycosuria, congestive heart failure, infections, ecchymoses and purpura, and peptic ulcer.[194, 1486, 1600, 1791, 1880, 2292, 2563, 2698, 3083] Similar changes occurred with the use of pred-

nisone and prednisolone, though edema and hypertension were much less common.[194, 275, 326, 864, 956, 2236, 2563, 2677, 2993, 3181, 3290] Several side-effects, considered to be unique for triamcinolone, included headache, dizziness, anorexia, nausea, bloating and distention, sleepiness, weakness, fatigue, leg cramps, tachycardia, erythema of neck and upper thorax, ecchymoses and purpura.[1052, 1364] In 32 older patients treated with triamcinolone, loss of water, sodium and potassium was marked, especially in patients initially edematous. Purpura occurred in two, weakness in two. Dosage ranged between 6.0 and 12.0 mg. daily.[2064]

Cushing's features, which had developed in half of the group while taking prednisolone, did not change in 60 patients treated with methylprednisolone. One of three patients with duodenal ulcer had an exacerbation of symptoms during treatment; all were on a strict anti-ulcer regimen. Three other patients had indigestion and abdominal pain, but normal roentgenograms of the upper gastrointestinal tract. There was no evidence of either water or electrolyte disturbance, and no significant weight gain or loss; no hypertension or diabetes mellitus developed.

In 18 patients treated with dexamethasone, there was no significant retention of sodium or loss of potassium. Carbohydrate tolerance was unimpaired after 10 weeks of therapy. The usual "minor" side-effects were seen, but no "major" or "unusual" side-effects.[438] The four major side-effects considered to be especially disabling and serious were peptic ulcer, compression fractures of vertebral bodies, mental disturbance and collagen-vascular disease.[434] Of 18 deaths associated with corticosteroid therapy, infection was the most common cause and was responsible for seven. Steroid therapy was considered to be directly responsible for 11 deaths, and probably hastened death in three more cases. In four cases, corticosteroid treatment was not responsible.[41]

Mental Disturbances. The reported incidence of various types of mental reactions associated with corticosteroid therapy averaged about 5%, but ranged up to 58%, with frank psychoses in up to 10%.[434, 3263] Most aberrations were transient and mild, and subsided with discontinuation of the hormone. A few patients required major psychotherapy. Suicide and attempted suicide were not rare. No mechanism has been delineated. Mental responses were considered to be "related to the psychological significance of the patient's illness and the symbolic value to him of an alteration in symptoms." Discontinuance of the steroid depended upon the severity of the reaction.[3263] Among 68 patients in whom psychiatric problems were common, all occurred in women, except for five cases of insomnia in men.[1486] Of 14 with depression, half were in or just past the menopause; three had episodes of disorientation, and two became agitated. Depressions were persistent but fluctuated in severity. Sedation and decrease in steroid dosage with psychotherapy were required, and sufficed in 13. Suicide or attempted suicide was reported.[2292]

Instances of acute panic of psychotic proportions[2406] and coma, hyperpyrexia, hypotension and, later, dysarthria, Parkinsonian tremor and muscular weakness were reported.[209]

Diabetes Mellitus. Temporary diabetes mellitus appeared after relatively large doses of corticotropin. Cortisone and related steroids sometimes aggravated diabetes, and also caused latent diabetes to become manifest. In some instances, latent diabetes mellitus, made severe by steroids, remained severe after therapy was discontinued. A lasting diabetes occasionally followed the use

of corticotropin,[2056] but with corticosteroid therapy, development of permanent diabetes mellitus was rare,[3263] although it was mentioned as a complication of prednisone [275, 326, 956, 2993] and triamcinolone therapy.[1358] Prednisone, 6-methylprednisolone and triamcinolone in comparative amounts produced effects on carbohydrate metabolism similar to those of cortisone.[1783] Glucose tolerance was impaired in four of five patients who had taken prednisolone for long periods prior to administration of dexamethasone. Carbohydrate tolerance of patients with rheumatoid arthritis was unimpaired after 10 weeks of dexamethasone therapy.[438] Cortisone administered to eight diabetics during a 24-hour period of insulin and food withdrawal increased their glycemia, insulin resistance and catabolism, but did not increase their ketonemia or decrease the carbon-dioxide combining power; evidently, cortical steroids did not contribute significantly to the development of diabetic keto-acidosis.[1610]

Purpura. Hemorrhagic skin lesions such as petechiae, purpura and ecchymosis, and a tendency to "bruise" with slight trauma, were noted singly or in combination more frequently with prednisone or prednisolone than with cortisone or corticotropin. The majority of such lesions were seen in women, and most commonly were located on forearms, wrists and dorsa of hands and fingers,[753, 803, 1764, 2239, 2260] Lesions of this type occurred in seven of 30 patients (23%),[803] 44 of 109 patients (40%),[2239] and 15 of 75 patients (20%).[753] No consistent correlation was found between capillary resistance and plasma concentration and/or urinary excretion of 17-hydroxycorticoids.[1764] Coagulation factors, capillary resistance and fragility, and serum electrophoretic patterns failed to demonstrate the mechanism of production of the hemorrhagic lesions.[2239] Rumpel-Leede tests indicative of increased capillary fragility were positive and sometimes remained so for months. Platelet counts and coagulation tests did not help to explain the phenomenon.[753] Prothrombin time and ascorbic acid concentration in the blood were also normal in seven other patients with purpura.[275] The subcutaneous bleeding from slight trauma was attributed to a lack of a normal hemostatic mechanism in the pericapillary tissues.[2239]

The clotting times of patients given corticotropin, cortisone or prednisone were, respectively, uninfluenced, slightly prolonged, or usually decreased. Thrombocyte counts were essentially unchanged.[818] A generalized erythematous dermatitis of bullous type attributed to prednisone was reported.[339]

Cardiovascular. No new information concerning cardiovascular complications appeared. Some conditions attributed to steroid therapy were due to the myocarditis or polyarteritis of rheumatoid arthritis.[2480, 2698] Hypertension, which often developed with the earlier steroid preparations, and especially with 9-α fluorohydrocortisone, decreased in many when prednisone or other newer steroids were given,[321, 326, 438, 1365, 2993] but congestive heart failure and cerebrovascular accidents were reported.[1486]

Salt and water retention and edema were much less common with the newer steroids.[275, 1052, 2993] Diuresis, with loss of water, sodium and potassium, followed the use of triamcinolone in older patients; the blood pressure was not affected in cardiac [2064] or noncardiac patients.[1365] One case of malignant hypertension with fatal cerebral hemorrhage followed prednisone therapy of diffuse systemic sclerosis.[608]

Vasculitis and Neuropathy. Severe vasculitis involving peripheral nerves, with clinical findings of severe peripheral neuropathy, developed in six R.A.

patients during steroid therapy.[1519] Of 10 patients with peripheral neuropathy, five had never received steroids, but four others developed the neuropathy within a month of discontinuance of steroids. Sensory changes preceded motor changes in the four patients who developed both.

Diffuse arteritis was considered to be a part of rheumatoid disease.[1355] Necrotizing arteritis occurred in four patients who had received cortisone; two had evidence of chronic hypercortisonism. No similar cases appeared in patients who had not received cortisone. Patients with rheumatoid arthritis and chronic hypercortisonism sometimes showed evidence of pan-mesenchymal reaction, with a necrotizing arteritis simulating periarteritis nodosa.[872, 1688, 2416, 3263] Polyarteritis nodosa occurred in four of 39 patients treated with prednisone; three of the four died. In three, the vasculitis may have developed while the dose was being decreased; in the fourth, dosage had been maintained at a constant high level. In one, death was due directly to the vascular lesion, since the patient died of hemorrhage from an aneurysm of an intrahepatic artery.[275] Fatal generalized vasculitis, with involvement of the mesenteric vessels and perforation of the colon, was reported in a patient treated with prednisone.[2993] Spontaneous gangrene of several fingers and toes was reported in a patient with rheumatoid arthritis and myxedema treated with prednisone and corticotropin. Postmortem examination revealed a polyarteritis and an obliterative endarteritis of the digital vessels and the vessels of the thyroid gland.[398]

Hypercortisonism. The syndrome of chronic hypercortisonism associated with excessive exogenous amounts of cortisone, hydrocortisone, prednisone or similar steroids was characterized by the cyclic occurrence of increased fatigability, emotional instability and generalized muscular and articular aching, in addition to the more commonly recognized side-effects. Depressed periods alternated with periods of "restless drive" and relatively little aching. Symptoms were most severe just before the next dose of corticosteroid was due, and were sometimes partially but only temporarily relieved by the next steroid dose or increase of dosage. Increased dosage was followed by accentuation of the cyclic symptoms. Exacerbation of rheumatoid arthritis due to inadequate doses of steroids or other factors, and flares due to overuse of damaged rheumatoid joints, had to be differentiated from the mesenchymal reaction of hypercortisonism. In the latter, the synovial reaction was minimal or not increased, and diffuse or generalized aching was referred to muscles and fibrous tissue rather than to joints. Cutaneous and subcutaneous hypersensitivity and hyperalgesia were also characteristic. Salicylates and physical therapy were of little help in hypercortisonism, but symptoms, especially the cyclic fatigue and aching, were benefited by rest.[2846, 2847] Others reported similar findings;[1687, 2693] the diagnosis of "steroid pseudorheumatism" was suggested.[2619] Of 128 patients with features of chronic hormonal overdosage, 18 (14%) had a mesenchymal reaction characterized by signs and symptoms simulating systemic lupus erythematosus, including positive L.E. preparations, fever in excess of 100° to 101° F. in over half, and evidence of renal involvement at some time in half. Transfusion reactions, leukopenia, encephalopathy, serositis, purpura, sensitivity to sunlight, pneumonitis, false-positive serology and phlebitis also occurred in one or more of the patients. Severe lesions resembling polyarteritis nodosa were observed in patients with peripheral neuritis, diffuse periarteritis, vascular occlusion, cutaneous ulcers, nephritis, fever, leukocytosis and hypertension. In some patients, severe reac-

tions were irreversible and death resulted.[2416, 2846, 2847] Prevention by use of low steroid dosages was easier than treatment of the condition after it had developed. Gradual reduction of steroid doses by small decrements at varying intervals was advised. A temporary increase of dosage for evidence of adrenocortical insufficiency was sometimes necessary. Additional rest, regular spacing of steroids at six-hour intervals, and encouragement and education of the coöperative patient in details of the problem greatly aided in management.[2416, 2846, 2847, 2977] Use of ACTH during the last few weeks of withdrawal was recommended,[2977] as was the use of iproniazid, an amine-oxidase inhibitor.[2693] [But it does not obviate the necessity of reducing the steroid dosage.—Ed.]

Corticosteroid Withdrawal Syndrome. A withdrawal syndrome was occasionally mentioned, but without reference to specific details. In nearly all of 19 asthmatic patients, the abrupt discontinuance of steroid therapy resulted in headache, nausea, vomiting, restlessness and muscle or joint pain, which subsided spontaneously in two to five days. No definite cause was determined.[450] [Mesenchymal reactions as described above have not been reported in asthmatics with chronic hypercortisonism.—Ed.] Corticosteroids induced dependence, and some patients developed all three classic signs of addiction: (a) tolerance, (b) emotional and physical dependence upon continued use, and (c) the abstinence syndrome. Psychologic reactions ranged from euphoria to depression to frank psychosis. Abrupt withdrawal led to serious depression [1283] and, in patients with R.A., usually to a prompt exacerbation severe enough to necessitate resumption of steroid therapy; gradual reduction, or the "weaning process," was more successful.[2977] [The withdrawal syndrome was not so specific in patients with R.A. as in those with bronchial asthma. Rheumatoid patients may be more prone to the mesenchymal-arteritis reaction described above. Rapid reduction or abrupt discontinuance of steroids because of an emergency such as hemorrhage from a peptic ulcer occasionally resulted in a syndrome of weakness, aching, tachycardia, fever and acute exacerbation of joint manifestations.—Ed.]

Effect on Development of Fetus. Implications arising out of observations that cortisone was a teratogenic agent in small experimental animals were discussed.[861] Early maturation and degenerative changes of the pancreatic islets were found in stillborn fetal rabbits whose mothers had been given adrenocorticotropin and cortisone from the nineteenth to the twenty-sixth day of pregnancy.[1847] Dosage of cortisone, period of gestation during which therapy was initiated, and genetic constitution of the animals were factors in determining occurrence of cleft palate without harelip in mice and rabbits.[861] One case of cleft palate without harelip was reported in a full term stillborn male baby whose mother had been treated with cortisone early in pregnancy.[1339] [Further experience has indicated that many apparently normal babies have been born of mothers treated with steroids before and during pregnancy.—Ed.]

Osteoporosis. Osteoporosis, with or without pathologic fracture, was one of the more common complications of steroid therapy.[275, 434, 1486, 2605, 3263]

Severe osteoporosis of the spine and ribs, found in four autopsied cases of Cushing's syndrome, was attributed to impaired osteoblastic function demonstrated by the histologic abnormalities of fracture callus in one of the cases, and was comparable to changes produced in experimental animals by administration of adrenocorticotropin or cortisone.[2831] Forty-eight steroid-treated R.A. patients with fractures were reported. Any amount of steroid sufficient to induce regression of an inflammatory process might suffice to lay the groundwork for a

fracture.[2605] In 68 steroid-treated rheumatoid arthritics, six vertebral compression fractures occurred.[1486] Pathologic fractures were reported in eight patients (21%) treated with prednisone; all but one were women, and six of the eight were over 50 year of age; seven of the eight had had R.A. for 10 years or longer. Vertebral, rib, pelvic and femoral fractures occurred.[275] Fractures occurred during triamcinolone therapy.[1052, 1358] The osteoporosis of R.A. was further aggravated by the antianabolic effect of adrenocorticotropin, exogenous cortisone or related steroids. Gonadal or anabolic hormones (androgen and/or estrogen) were believed to prevent, counteract or control the adverse effect of the cortisone or cortisone-like steroids used in treatment of R.A. An amount sufficient to prevent hypercalciuria, which indicated adverse cortical effect on bone, was recommended. Combination of androgen and estrogen appeared to be the most potent and practical therapy now available.[2505, 2511, 2512] [Although widely used, it has not been generally satisfactory, and does not substitute for reduction of steroid dosage in rheumatic arthritis. A more extensive review of osteoporosis and details of therapy are given elsewhere in this Review.—Ed.]

Infection. Infections of a serious nature complicated steroid therapy.[41, 275, 860, 1115, 1486, 1635, 2292, 2698] Tuberculosis was sometimes activated.[282, 283, 2632, 3365] One of six deaths among 39 R.A. patients treated with prednisone was due to pneumonia and meningitis.[275] Infection was the most common complication, and pneumonia was responsible for six of 18 deaths.[41] Severe infections were confined to debilitated patients, but ambulatory, vigorous patients were frequently afflicted with superficial fungus infections, paronychiae and furuncles. Abscesses were fewer after initiation of oral steroids. Fifty-three infections occurred in 68 patients treated with cortisone during a five-year period.[1486] Five of 15 fatal cases were due to infection.[2292] After four years of cortisone therapy, a 34 year old woman with R.A. developed acute adrenal insufficiency soon after the onset of pneumonia.[530] Suppuration in joints following aspiration of fluid or intra-articular steroid injection warranted careful precautions any time a joint was entered.[3087]

Adrenocortical steroids given over a brief period to patients critically ill with an infectious disease sometimes brought about dramatic improvement without harmful side-effects, but they were advised only when an effective antimicrobial drug was given at the same time.[860, 2556] Large doses of steroids altered host resistance of infection by (1) suppression of antibody formation, (2) decreasing movement and phagocytic activity of leukocytes, and (3) alteration of function of the reticuloendothelial system. In allergic reactions or other disease states where inflammatory and vascular changes were undesirable, as in periarteritis nodosa, this anti-inflammatory effect was beneficial.[1120] However, the value of corticosteroids in the management of infections, except in instances of manifest adrenal insufficiency, was still uncertain.[1635]

Tuberculosis and virus infections were considered to be a contraindication to the use of adrenocorticotropin or adrenocorticosteroids. Superinfection by normally nonvirulent organisms, especially when antibiotics were also given, was not unusual.[2698] However, in tuberculosis, the use of corticosteroids with tuberculostatic therapy (1) suppressed the state of hypersensitivity to the bacillus or its products, (2) suppressed hypersensitivity of the patient to the tuberculostatic drugs, and (3) improved resistance of the patient indirectly by ameliorating the stress of toxemia.[282] The possibility of reactivation or precipitation of active

tuberculosis by corticosteroid therapy was again emphasized.[283, 2632, 3365] Positive tuberculin reactions developed in 20 of 24 patients with various diseases during therapy with cortisone or prednisolone in moderate dosages, though corticosteroids in high dosages suppressed positive tuberculin reactions. In low or moderate dosages, steroids sometimes actually restored a tuberculin reaction suppressed by age, infection or adrenal deficiency.[3126] [The evidence to support this statement was inadequate.—Ed.] Effects of cortisone on the inflammatory reaction studied in the rabbit ear chamber were shown to be suppression of the initial vasodilatation, rather a vasoconstriction with prevention of adherence of leukocytes to the endothelium.[3860] Cortisone lowered the body defenses of the guinea pig by depressing the phagocytic activity of the reticuloendothelial system, the total white blood cell count and the relative number of lymphocytes in the blood and the gamma globulin level in the serum.[2277] The total leukocyte count decreased during the first three weeks, and then rose above normal during the fourth and fifth weeks of treatment. These changes were due to a sustained fall in the number of lymphocytes, and a gradual rise, after the first week, in the number of pseudo-eosinophils.[2276]

Prednisone, prednisolone, cortisone and hydrocortisone interfered with host defense mechanisms and with the chemotherapeutic effect of broad spectrum antibiotics when given in massive doses to mice infected with streptococci, but not when given in low doses which, on a weight basis, approximated those used in human medicine.[1015] The hemolysin response in the rat after a single intraperitoneal injection of sheep erythrocytes was characterized by a significant reduction in antibody production when cortisone was given for two or more days before antigen injection, and a maximal reduction when it was also given on the same day as the antigen. Cortisone given after injection of antigen did not cause significant reduction in antibody production.[232] Further study of the same hemolysin response in the rat found that cortisone administration affected the antibody response less after a large dose of antigen than after a small one.[233] A significant reduction of circulating antibodies, as shown by the H-agglutinin response in the rat to a single intraperitoneal injection of *Salmonella typhi H* vaccine, followed administration of large doses of cortisone for six days before injection of the antigen.[234] That the antibody-reducing effect was not affected by particle size of the antigen was shown by antigens consisting of (a) killed bacteria, and (b) purified flagellar protein in a comparatively low molecular form.[263] Cortisone therapy produced no alteration of any globulin fraction of rat sera.[209] The antibody-reducing effect of cortisone was significantly greater in splenectomized than in sham operated rats.[232] Spleen or thymus cells from intact donor rats had a protective effect on antibody production against cortisone, suggesting that these cells produced a factor or had a cellular function essential for an initial, cortisone-sensitive phase of antibody production process.[96] Of seven crystalline C-21 steroids tested, cortisone, hydrocortisone, corticosterone and 11-dihydrocorticosterone inhibited the production of circulating hemolytic antibodies in the mouse.[2271]

A common mechanism might be involved in the suppressive action of steroids on antibody synthesis, the local inflammatory response, and the ability of macrophages to break down and dispose of foreign materials. It was uncertain whether phagocytosis and digestion of antigen by macrophages were necessary preludes to antibody formation, or whether these processes removed and prevented a major portion of injected material from exerting its antigenic capacity.[3058]

Gastrointestinal. These varied in severity, but were considered to be among the most common serious complications.[275, 326, 454, 1110, 1161, 1235, 1236, 1409, 1486, 1624,

[1698, 2675, 2698, 2993, 3173, 3263] Development of peptic ulcer or reactivation of peptic ulcer often followed use of corticosteroids.[1235, 1409, 1624, 1698] It was again reported that ACTH also induced peptic ulcers,[1236, 1409, 1698, 2698, 3263] although ACTH was only slightly if at all ulcerogenic.[2675, 3290] [Factors of dosage and host response are important variables.—Ed.] Use of ACTH with phenylbutazone greatly increased the risk of peptic ulcer.[1698]

Symptoms of peptic ulcer in patients receiving corticosteroids were sometimes so masked that first indications were hemorrhage or perforation.[936, 1161, 2675] Perforations of gastric and duodenal ulcers, masked as well as symptomatic, were also reported.[434, 970, 1225, 1420, 2320, 2722] Incidence of peptic ulcer increased significantly when prednisone or prednisolone was initially used or substituted for cortisone, hydrocortisone or adrenocorticotropin.[275, 322, 326, 738, 802, 848, 936, 970, 1110, 1225, 1420, 1624, 2329, 2722, 2993, 3263, 3342]

Ulcers sometimes occurred during the first few weeks of treatment; in other instances, not until the second or third year of therapy.[3263] As with cortisone therapy, hemorrhage was sometimes preceded by epigastric pain or nausea, but often was the initial manifestation.[434, 738, 802, 848, 1110, 1486, 2993] Six of 39 prednisone- and prednisolone-treated patients had peptic ulcers;[275] including these, 12 peptic ulcers occurred in 48 patients, an incidence of 25%.[848, 1429] Among 117 R.A. patients treated with corticosteroids, 31 (35%) of 88 given prednisone developed peptic ulcers.[1624] Of 69 patients treated daily for at least half a year with 5 to 15 mg. prednisone or prednisolone, roentgenographic examinations showed peptic ulcers in 19%. At necropsy the incidence of peptic ulcers in 31 R.A. patients not treated with corticosteroids was about 10%.[1110] [Necropsy statistics are apt to be misleading. They are weighted toward increased frequency because of the number of acute ulcers developing just before death.—Ed.] Among 156 prednisone- or prednisolone-treated patients, 48% had dyspepsia. X-ray examination of 45 revealed seven with peptic ulcers. In five other patients, hemorrhage or perforation of an ulcer developed.[2993] More new ulcers developed with large doses of cortisone or prednisone than with smaller doses (less than 50 mg. cortisone or 15 mg. prednisone). Patients with long-standing R.A. were more prone to develop peptic ulcer.[1698] A prior history of peptic ulcer was obtained from a majority of patients who developed digestive disturbances during prednisone therapy.[322] [History of proved peptic ulcer should make one cautious in prescribing prednisone or prednisolone.—Ed.] Intramuscular administration of prednisolone acetate was reported as greatly lessening gastric disturbances.[3291] Pretreatment x-ray investigation of the gastrointestinal tract was recommended.[970]

Prophylactic aluminum hydroxide gel preparations and semibland diets seemed to be warranted in view of the frequency of digestive disturbances, and of the effect of steroids on gastric secretion.[322, 324, 326] Use of antacids with each divided dose of prednisone and prednisolone reduced the incidence of roentgenographically demonstrated peptic ulcer to 3%.[322] Triamcinolone was believed to have minimal ulcerogenic effects.[1364, 1365, 3429] Peptic ulcers healed on usual ulcer therapy in six to 12 patients receiving triamcinolone,[1052] but hemorrhage from the upper gastrointestinal tract[404] and perforation were reported.[1358] Little difference in ulcer symptoms appeared in patients transferred from prednisolone to methylprednisolone therapy.[488] Preliminary studies on dexamethasone in 12 patients did not reveal the development of any recent peptic ulcers.[438] [This has not been borne out by more recent experience.—Ed.]

Ulcer formation in corticosteroid-treated patients involved three possible mechanisms: (1) increased gastric secretion of acid and pepsinogen, (2) depression of gastric mucous secretion, and (3) depression of the repair process.[1486] Increase in hydrochloric acid and pepsinogen secretion and increase in uropepsin excretion occurred in man during ACTH or cortisone administration.[1234, 1235, 1253]

Others did not find that prednisolone increased gastric secretory volume or acidity.[815, 3342] Intravenous administration of ACTH, hydrocortisone and prednisolone in an acute study on 53 patients failed to produce any increase during a six-hour period in the rate of flow of gastric juice, in its free and total acidity, and in the rate of pepsin secretion. Adrenocorticotropin and adrenal steroids were not gastric secretagogues; their role in ulcerogenesis remained unclear.[815] Eight-hour intravenous ACTH, hydrocortisone or prednisolone infusions caused no change in concentration or output of gastric hydrochloric acid or pepsin.[1442] Six-methylprednisolone caused less increase in uropepsin excretion than did prednisolone or triamcinolone.[1782]

Steroid-induced peptic ulcers were found predominantly in the antrum of the stomach, and on x-ray examination were shallow and flexible. Peristaltic waves often passed through the bases without interruption. Fibrosis and rigidity of the stomach wall were occasionally seen. Abdominal tenderness was usually absent.[424, 1046, 1409, 1429, 1502, 1510, 1624, 3173] Hemorrhage and perforation were not unusual.[848, 1409, 1624, 2329, 2722]

Peptic ulcer was observed radiographically in 36 of 117 patients (31%), but in only 9% of nonsteroid-treated R.A. patients and in 5% of nonrheumatoid controls. Four ulcers were reactivated; 32 were of recent origin. Thirty-one of the 36 were gastric and five duodenal. Incidence was about the same in men (six of 22) as in women (30 of 95).[1046, 1624] The histologic findings were those of acute ulceration, with little evidence of healing or repair.[1429]

A steroid-induced prepyloric gastric ulcer in a previously healthy 23 year old male medical student was not associated with significant changes in gastric secretion of acid and pepsin.[1441] Peptic ulcer patients had no greater adrenal cortical response to ACTH than did nonulcer patients.[708]

The hazard of perforating the colon in chronic ulcerative colitis was not increased by administration of ACTH or steroids; no significant difference in cellularity, fibroblastic proliferation or leukocyte accumulation was noted between the histologic material of the presteroid era and that of the steroid era. Cases with "masked symptoms" were also encountered before the steroid era, as were giant ulcerations.[1179] Three fatal perforations of the gastrointestinal tract, two in the cecum and one in the second portion of the duodenum, occurred during administration of corticosteroids. None of these patients had given a history of pain or presented any previous evidence of a lesion in these areas.[1738] Fatal perforation of the colon on the basis of an extensive generalized vasculitis was reported in a rheumatoid patient receiving prednisone.[2993]

Induced Adrenal Cortical Insufficiency. Suppression of endogenous adrenal cortical function occurred during administration of the corticosteroids (cortisone, hydrocortisone, prednisone, prednisolone, triamcinolone, 6-methylprednisolone, dexamethasone). Manifestations varied from those of mild or questionable insufficiency to the characteristic acute crisis. Symptoms of insufficiency usually appeared after rapid reduction of dosage or discontinuance of the corticosteroid.[199, 224, 1357, 1486, 3330] The potential hazards of surgery to

patients receiving corticosteroids were affirmed by the number of papers referring to decreased endogenous adrenal function, with impaired or absent ability to respond to stress.[96, 199, 833, 1028, 1094, 1141, 1357, 1378, 1402, 1486, 1504, 2843, 3277] [Suppression of pituitary activity also limits the ability of patients receiving adrenocorticotropin to respond to stress.—Ed.]

Steroid-induced adrenocortical insufficiency has become such a serious complication that every physician should record in the routine history whether a candidate for operation has ever received ACTH or adrenocortical steroid therapy.[1378] Adequate preoperative preparation, with intravenous cortisol during and adequate corticosteroid therapy after surgery, was recommended.[833, 1141, 3330] A survey of a private and semiprivate general surgical services showed that 5.6% of 2,490 patients coming to the operating room had received corticosteroid treatment at some time. Two of the 76 patients had adrenal cortical insufficiency following operation. One had received the regular preoperative steroid preparation; the second had not. Both recovered following intravenous hydrocortisone administration.[1141] Fifteen of 28 patients (53%) who had received steroids developed a shock syndrome, refractory to blood replacement, during or immediately after a surgical operation. During the same period, 25 patients with the same diagnoses who had never received steroids were operated upon without a single episode of shock. Six of the 15 patients with shock had been given the usual preparation with depot cortisone. Eleven patients given ACTH were carried through their operative procedures without incident.[1378] Preoperative preparation with adrenocortical steroids, and intravenous hydrocortisone during surgery, protected 36 patients on long-term treatment with either adrenocortical steroids or ACTH from acute adrenocortical insufficiency.[2422] Although cortisone in doses of 37.5 to 50 mg. was indicated for full substitution therapy, in times of stress this was inadequate, and intravenous hydrocortisone was necessary.[1357]

Preoperative preparations varied in some minor details, but consisted essentially of giving the patient about as much exogenous cortisone as his own adrenals would make were their function not temporarily suppressed.[1402] For elective operations on patients receiving steroids or ACTH, 100 to 200 mg. of cortisone were given intramuscularly 48 hours and 24 hours before operation, and about half or all of this dosage again on the morning of operation; patients who had received steroids or ACTH within 18 months of the surgery also required this treatment. The usual oral steroid doses were continued in addition to intramuscular cortisone. For emergency procedures, the immediate intramuscular injection of 200 mg. of cortisone and intravenous infusion of hydrocortisone hemisuccinate or hydrocortisone free-alcohol during the operation were recommended. Corticosteroids should not be discontinued before or after operative procedure. The short half-time of corticosteroids made oral or intravenous administration necessary every six to eight hours; intramuscular administration was needed at least once and sometimes twice daily. Intravenous hydrocortisone, in amounts of 100 mg. or more during operation, was usually recommended. Postoperative management included cortisone or other corticosteroid intramuscularly for the first few postoperative days, then orally as tolerated or required by the patient.[199, 750, 1028, 1094, 1141, 1378, 1402, 2060, 2422]

Management of patients on ACTH was more difficult; the preparation was continued over the operative period, and alterations in dosage were dictated by the daily excretion of 17-hydroxycorticosteroids. Hydrocortisone was given intravenously if any signs of acute adrenal insufficiency developed.[2422] Daily administration of 20

units of ACTH intravenously or 40 units of ACTH gel or zinc-ACTH was recommended for a week or so preceding any elective surgical procedure for patients who had been on adrenal corticosteroid therapy.[750] Intravenous ACTH stimulation prior to surgery was preferred to preoperative cortisone administration.[96, 1378, 2843] [The uncertainty of response in a given patient detracts from the value and reliability of this procedure.—Ed.] One such routine consisted of daily eight-hour infusions of 20 units of ACTH until an 80% drop in the eosinophils in the first four hours occurred. On the day of surgery, a constant infusion at the rate of 20 mg. of ACTH each eight hours was given. On the first postoperative day, 20 mg. ACTH were injected intramuscularly every four hours, and dosage was reduced by one such injection each postoperative day.[1378] Both hydrocortisone and ACTH could be used during operation and in the postoperative period.[1141] Preoperative reactivation of the adrenal gland by intramuscular injection of corticotropin gel and continuous ACTH infusion during the operation were combined with intravenous, intramuscular or oral corticosteroids before, during and after surgery in 20 patients undergoing 25 major operative procedures requiring general anesthesia. No patient presented any evidence of adrenocortical insufficiency.[1486] [The first and most important rule is not to stop any current steroid program. Second, in the event of any uncertainty of adrenal cortical function, give supplements.—Ed.]

Excretion of total 17-hydroxycorticosteroids during the second day after operation was nearly four times the preoperative excretion in 52 elderly nonsteroid-treated patients. Values were higher in men than in women, and tended to be lower in older members of the group.[2375] Of 22 patients who had been on long-term treatment with corticoids, responsiveness to ACTH was delayed in 19; there was no correlation between the daily dosage of steroid or the duration of treatment and the adrenocortical response to ACTH.[1830]

Other. Aseptic necrosis of bone, especially in weight-bearing joints, occurred among corticosteroid-treated R.A. patients. Hips were most frequently affected, though similar changes were observed in knees, ankles and subastragalar joints. Marked relief of pain resulted in greatly increased use of affected joints. They were exposed then to unusual trauma, and this resulted in the development of aseptic necrosis or Charcot-like deterioration of weight-bearing joints.[854] Nodular panniculitis developed after prednisone therapy.[3063]

Plasma levels of 17-hydroxycorticosteroids rose from 200 to 400% during pregnancy. Since only a part of the plasma 17-hydroxycorticosteroids could diffuse into the tissues, the amount of free cortisol that appeared in the urine was a measure of available cortisol. This increased about 100% during pregnancy. Disparity between the increase in nondiffusible protein-bound 17-hydroxycorticosteroids and that which was freely diffusible suggested that the nature of the proteins that bind cortisol might change during pregnancy.[3288] Some patients needed less or were able to discontinue steroids during pregnancy.[1508, 2676]

Diet and Vitamins. A review of the nutritional aspects of R.A. again revealed no etiologic relationship. A nutritionally sound diet suited to the needs of a chronically ill patient with adequate protein, mineral and vitamin content was advised. Caloric content was adjusted to individual need.[2566]

Correction of Anemia. Transfusion therapy was of temporary, if any, benefit, and usually did not justify the inherent risk. Administration of blood or plasma was only part of a broad basic program tailored to the patient's status.[882]

The failure of oral iron (ferrous gluconate) to correct the anemia of R.A. was reaffirmed, but mild improvement followed short-term intravenous and intramuscular iron therapy. The rise in hemoglobin was sustained for the 14 weeks of observation.[2150]

Psychotherapy. Emotional and psychologic aspects were of "first importance," but etiologic relationships were regarded as controversial.[2555] Study of the motor activity of 18 arthritic patients and their nearest siblings indicated that those with arthritis had been overactive as children but inhibited later in life (prior to the illness). The siblings, however, began with normal or inhibited motor function and were able to use their motor apparatus for instinctual discharge in later life.[653]

The attack of chronic physical disability on personality, with the attendant need for reorganization, was reviewed briefly in nontechnical terms. Emotional support of the patient at the end of the acute phase of a chronic illness, discussion of depression-producing anxiety (Will I be accepted? How dependent will I be?, etc.), acceptance of realistic depression, and the associated irritability and hostility, were important in helping the patient to work through readjustment and to prepare for physical rehabilitation. Orientation of the family and preparation of the patient for home environment were imperative in establishing healthy relationships between patient and relatives, and between patient and physician. A brief follow-up social visit at home was an "excellent investment" in maintaining a high motivation.[1909] [This is an excellent review of the psychology of physical disability.—Ed.] Assistance from a medical social case worker facilitated this phase of treatment.[1992]

Vaccines and Fever Therapy. Artificially produced febrile reactions were associated with increased plasma 17-hydroxycorticosteroid levels in humans and dogs;[559, 801, 2809] this plasma-steroid elevation reflected increased adrenocortical secretory activity, but the mechanism was uncertain. This adrenocortical response was blocked with aminopyrine, mildly suppressed by salicylates, but uninfluenced by reserpine.[164, 2057] No clear evidence of increased skin sensitivity to bacterial antigens was demonstrated in patients with R.A., and only eight of 64 vaccine-treated patients showed unequivocal improvement.[3034] Intravenous polyvalent typhoid vaccine (T.A.B.) fever was used in 100 cases, with the following results: 54% complete remission, 20% major improvement, 16% moderate improvement, and 6% progression of disease. Best results were noted in early cases (Stages I and II).[2809] [Stage of disease and follow-up period were not specified. Reported results were comparable to those of many other agents.—Ed.]

Chrysotherapy. Debate on the value of chrysotherapy continued, but the continuing use of soluble gold salts by experienced and critical rheumatologists suggested merit.[463, 527, 1051, 1053, 1623, 1917, 2608, 2866, 3229, 3421] Since the anticipated superiority of steroid therapy had not yet been realized, chrysotherapy was worthy of reconsideration.[1053]

Indications and Contraindications. Active R.A. responding unfavorably to conservative management was regarded as the prime indication for gold therapy.[1053, 1623, 1917] [This indication is more easily stated than determined. Concepts of "activity" and "conservative" management are not well standardized.—Ed.] Early cases responded most favorably, but active cases at any stage might benefit. Age alone did not preclude chrysotherapy.[1053, 1623, 1917] Known prior gold toxicity was the important contraindication to gold therapy noted, but systemic lupus erythematosus, significant renal, hepatic or hematopoietic dysfunction, and general debility also mitigated against gold therapy. Chronic skin eruptions were not contraindications. [Some of us do not agree.—Ed.] Chrysotherapy had to

be modified in pregnancy, but a pregnant patient might receive gold without detriment to herself or her child.[1053]

Preparations. Gold sodium thiomalate (Myochrysine) and gold sodium thioglucose (Solganal), both soluble salts containing 50% gold, were the most generally used preparations.[1053, 1917, 2480, 2866] Gold sodium thiosulfate and gold calcium thiomalate were also used.[1566, 2608]

Mode of Action. The mode of action of gold salts remained unknown, but effects were exerted at the tissue level through influence on cell metabolism.[1053] The reticuloendothelial deposition of colloidal gold preparations was reaffirmed by various technics, including in vivo human studies.[917, 1100, 2494, 2719] In rats, colloidal radiogold Au^{198} did not form a metaloprotein complex.[2234] Pituitary and adrenal factors [not detailed.—Ed.] regulated its uptake by the reticuloendothelial system.[2494] The distribution and excretion of noncolloidal gold restudied by radioisotopy with labeled calcium aurothiomalate discovered highest radioactivity in the kidney; no other organ showed major activity.[1566]

Method of Administration. One of two test doses of 10 or 25 mg., followed by weekly intramuscular injection of 20 to 50 mg. of gold salt, were advised. Optimal maintenance therapy was 20 to 50 mg. doses at varying intervals,[463, 1051, 1623, 1917, 2480, 2608, 3229] but equal therapeutic efficacy was claimed for the lower maintenance doses.[3229] Therapeutic failures in patients on this "standard" program were associated with high urinary gold excretion rates, and an increased maintenance dose was advised.[2866] [The lack of toxicity with higher doses reported here does not conform to the experience of many observers.—Ed.]

Results. Gold salts intramuscularly afforded a 20% better chance of major improvement or remission in a controlled study for 507 gold-treated arthritics than for 566 nongold-treated controls. [The duration of disease was at least three months; duration of therapy was not stated.—Ed.] More than 300 mg. of gold salt had to be given to influence the arthritis.[1917] With urinary gold excretion rate as a guide to dosage, a remission rate was obtained of 82% in 85 cases, which contrasted with that of 66% in 140 cases receiving (conventional) gold dosage.[2866] [Unfortunately, results of chrysotherapy were not analyzed by the use of existing criteria for diagnosis, progression, therapeutic response or functional capacity.—Ed.]

Toxicity. Toxicity of 4 to 51% of cases was reported; the average was 37%. Discontinuation of therapy was necessitated by toxicity in 3 to 24% (average, 9%).[409, 410, 1053] Metallic taste, pruritus, blepharitis, stomatitis, urticaria, erythematous and lichenoid dermatitis, exfoliative dermatitis, agranulocytosis, anemia, nephritis, hepatitis, thrombocytopenia, encephalitis, peripheral neuritis and colitis were cited as toxic reactions to gold.[316, 408, 665, 1053, 1381, 1917, 2073, 2216, 2469] Toxicity was related to decreased urinary gold excretion.[2866] No deaths directly attributed to gold treatment were reported. [This in itself represents refined technics in use of gold with continued experience.—Ed.] Three cases of unexplained sudden death in patients receiving large doses of gold were studied histologically for gold in the central nervous system; none was found.[1138]

Five of eight cases of "gold dermatitis" were due to skin sensitivities to sesame oil; continued gold therapy with the same gold salt prepared with olive oil was uncomplicated.[190] Asymptomatic ocular chrysiasis with histologically proved gold deposits in the bulbar conjunctivae and diffuse bimicroscopic deposits in the conjunctivae and cornea was observed in a patient who had received 7,970 mg. of various soluble gold salts over a 10-year period.[2552]

Dimercaprol (BAL) produced three remissions in a patient with gold throm-

bocytopenia which had failed to respond to ACTH;[1381] both agents were recommended for management of gold toxicity.[463, 1053, 2469, 2608] [The ultimate value of chrysotherapy in R.A. is still unsettled after more than 25 years of clinical use. The gold salts continued to survive "the test of time," and their popularity revived as the application of steroids became more selective. Controlled studies with existing methods are still needed.—Ed.]

Miscellaneous Agents. Antimalarial compounds evoked a critical interest.[137, 605, 914, 1042, 2538, 2692] Chloroquine and hydroxychloroquine appeared to be less toxic than the earlier preparation.[605, 913, 2692] Improvement was reported in 50 to 97% of 1,092 reported cases treated with these drugs. Treatment periods varied from one month to four years.[1080] Two small scale, short-term, well controlled studies indicated that, statistically, chloroquine possessed some antirheumatic activity.[471, 1051] Clinical effect was rarely apparent in less than two weeks at doses of 250 to 500 mg. daily. Toxicity occurred in 30 to 40% of patients;[137, 471] effects observed were nausea, epigastric burning, vomiting, leukopenia, skin rashes (including exfoliative dermatitis), ocular disturbance due to corneal changes, acute toxic psychosis, and electrocardiographic T wave inversion.[471, 472, 1224, 3406] The drug did not influence adrenocortical function.[2777] [Antimalarials seem worthy of more detailed long-term investigation. They may be helpful in mildly active R.A. Evidence for an anti-inflammatory effect is meager. In many patients, continuous therapy for a year or more seemed to have no influence whatever on the course of the disease. Long-term controlled trials have not been reported. We do not share the enthusiasm of a few advocates of this therapy. At present, its value remains to be established.—Ed.]

Uncontrolled studies of muscle relaxants and tranquilizing agents, usually in conjunction with corticosteroids, have failed to demostrate anti-inflammatory properties.[1140, 2746, 2870, 2871, 2956] Claims of significant relief of secondary fibrositic symptoms were made.[1140, 2746, 2870, 2871, 2956] These agents appeared to be most effective against emotional tension or anxiety, a frequently troublesome aspect of the patient afflicted with a musculoskeletal disease.[231, 2746, 2956] [The enthusiasm, medical and social, which these agents received has waned. The emphasis is now on the effects which "relax skeletal muscle," a phenomenon difficult to gauge objectively and undoubtedly influenced by the psychic factor.—Ed]

Iproniazid (Marsilid), a euphoria-producing amine oxidase inhibitor, had little objective effect on the joint manifestations of R.A.[151, 353, 2688, 2691] Its effects on subjective manifestations, especially depression and tolerance of the disease by the patient, were favorable.[151, 2691] Hypothecations on the relationship of amines to the mechanisms of symptom production, and the effects of iproniazid on these, were presented.[2683]

Temporary early objective improvement was observed with nitrogen mustard therapy, but results could not be sustained. [Nonspecific adrenal cortical stimulation was postulated. Another mechanism is antihyperergia.—Ed.] Combined "low dose" intravenous ACTH and nitrogen mustard therapy produced improvement in 88% of 263 patients.[2689] Intra-articular nitrogen mustard as a supplement to intra-articular steroids caused joint inflammation to disappear for from one to two years in 37 of 106 cases, and for from six to nine months in an additional 35 cases.[2690] [These are excellent results, if confirmed. This study was without controls. There is currently little interest in this therapy.—Ed.]

Para-aminobenzoic acid and salicylate mixtures,[2956] para-aminosalicylic acid (PAS),[1380] salicylazosulfapyridine (asulfidine),[3024] hesperidin-ascorbic acid mixture,[3231] physostigmine-salicylate and atropin mixture,[2493] probenecid,[965] citrate

iontophoresis,[671] fresh ox bile,[2237] placental sera and sera from pregnant women [1216] were reportedly beneficial agents. Results with nikethamide were divergent; all of 38 Africans in Bechuanaland responded well to treatment,[2206] but no significant response was observed in 26 patients treated in New York City.[1105] Dipyrone [2165] and cysteamine [309] were of no symptomatic value.

Individual short-term, double-blind studies of the effects of manganese and pendiomide (a ganglionic blocker) on the clinical features of the disease gave negative results.[225, 1561] [As expected, "dramatic results" do not usually occur if a reasonable control is part of the drug test design.—Ed.] A salicylate-mephenesin preparation was thought to be responsible for a nonfatal case of thrombocytopenic purpura.[2404]

Physical Therapy. The inclusion of a physical therapy regimen in the total management of the rheumatoid patient received reëmphasis.[217, 218, 880, 1341, 1838, 2453, 2454, 2490, 2651, 3142] [This return to conservative measures attested to our current knowledge of the inadequacies of systemic drug treatment. The favorable symptomatic response to certain medication did not halt joint damage, nor did it obviate the need for physical treatment.—Ed.] Early treatment was thought to produce optimal results.[1838, 2453, 2801] A detailed prescription for daily, home-oriented treatment was recommended by most authors.[217, 1223, 2453, 2454, 3142, 3346] Although the details varied, preliminary heating, followed by active (or active assistive) exercises, was included in recommended programs; the selection of the heating modality and specific exercise planning were discussed in detail.[218, 1223, 1341, 2453, 2454, 3346] Multiple factors influenced these selections, but neither articular nor general rheumatiod activity contraindicated all physical therapy. Pain and joint inflammation were guides to the type of treatment. Orientation of the patient and follow-up examinations helped to motivate patients to maintain their home treatment.[2341, 2453]

The effectiveness of local heat in relieving pain was attributed, at least in part, to an increased blood flow, which in turn increased the tissue oxygen available and removed noxious metabolites.[1772] Increased local blood flow was augmented (from an average of 33 to 50 ml./100 ml./min. in six patients) by release of general sympathic vasomotor tone.[2569] Paraffin wax baths facilitated an earlier return to work than did other forms of heat.[1838] [No data were given.—Ed.] Continuous immersion and dip immersion of the hand in paraffin at 124° to 129° F. raised the skin temperature to 111 or 112° F. without discomfort to the patient. This effect was more prolonged with continuous immersion than with the dip-and-wrap technic.[2979] Cold packs increased joint mobility limited by pain.[2568] ["Radiographically abnormal joints" and contractures were treated without an exercise program. Perhaps cold application should be evaluated further.—Ed.] The need for critical observations on the clinical application of microwave diathermy was voiced.[2184]

Ultrasound was a "safe therapeutic measure when applied under the limits of recognized dosage and in accordance with contraindication."[1041] In "arthritides" the results were least remarkable.[2391] *In vitro* tendon, oriented parallel to the ultrasound field, developed an irreversible increase in extensibility and a reversible increase in water content.[1121] Biologic effects of ultrasound were reviewed.[147, 203, 1058, 2626] Controversy over its "segmental application" to the autonomic nervous system continued.[212]

Radiation Therapy. Peripheral rheumatoid arthritis was not significantly improved by x-radiation.[1702] [The third negative controlled study! One of us

(H.W.) tried this in six patients with peripheral R.A., with negative results. Kersley noted improvement of peripheral joint arthritis when patients with ankylosing (rheumatoid) spondylitis were radiated over the spine, and also improvement in the pain of osteoarthritis treated with high voltage radiation in tissue doses ranging from 500 to 2,000 v.—Ed.] The current medical applications of electromagnetic energy were briefly reviewed.[315]

Occupational Therapy. General recognition that occupational therapy is an integral part of total patient rehabilitation was again urged. The training of patients in purposeful activities of self-care and daily living was occupational therapy.[1496]

Spa Therapy. The history and development of "sauna bath" and its physiologic effects were reviewed.[1855] Hydrotherapy at an Eighteenth and Nineteenth Century English spa was described.[97] [This charming paper delightfully exposes the "past" foibles of physicians and spa patrons alike.—Ed.] No evaluation of this type of treatment appeared.

Nonsurgical Orthopedic Measures. Advocates of splints and casts continued to record uncontrolled favorable results with various technics of joint immobilization.[1678, 1683, 3028, 3029, 3065] The therapeutic aim of preventing joint deformity by joint rest, with the attendant relief of pain, inflammation and muscle spasm, and removal of postural and gravitational forces, was the general rationale.[1678, 1683, 3029, 3065] Regression of the systemic illness and arrest of the articular spread by attention to joint immobilization were claimed [1683, 3029] [but not proved.—Ed.]. "Active immobilization," i.e., continued use of the extremity with the immobilization of joints, was stressed.[1678, 1683] Arthritic contractures without marked bony changes were improved by gentle, repeated stretching under local anesthesia, but aggressive manipulation under general anesthesia was not advised.[1488] Technics of joint immobilization, including descriptions of two lightweight, water-resistant plastic casting materials, were reported,[385, 1678, 3028, 3065] but specific schedules for re-application of casts were not detailed.

Surgical Orthopedic Measures. Palliative procedures included operations on rheumatoid nodules, bursae and tendon sheaths, as well as joints.[183] Although major surgical procedures were best done when the disease was "burnt out," activity of the disease had little effect on the outcome of surgery.[127, 675, 1347] [We are inclined to agree with the latter comment. If operative procedures in all cases are postponed until disease activity subsides, many patients who could benefit will be excluded. It is difficult to determine with certainty when the disease is "burnt out." Motivation of the patient is more important than joint inflammation.—Ed.] The importance of motivation was stressed, and it was suggested that motivation could be assessed by achievement level prior to disability.[675] Corticosteroids were permitted earlier, as was more successful postoperative physical therapy, and these measures did not interfere with wound healing or increase the incidence of infection.[1347]

Improvement in a single patient with advanced R.A. following "extended lumbar sympathectomy" [1412] led to the use of this procedure in six additional patients (three R.A., three osteoarthritis). Relief of pain and improvement of function occurred in follow-up observations ranging from four to 24 months.[1413] [This procedure must be considered as experimental.—Ed.]

Hip. The process of repair of articular surfaces following arthroplasty of the hip were studied in detail in 15 patients, four of whom had R.A., who required re-

operation. Microscopic and biochemical studies confirmed the formation of fibrocartilage, apparently arising from subchondral bone, in those instances where good collateral circulation was present, and all devitalized bone and cartilage had been removed at the original operation.[3151] Experimental studies with whole-layer skin used as interposing membrane in the hip of the cat demonstrated cartilaginous metaplasia occurring over the weight-bearing area of the joint, with histologically recognizable hyaline as well as fibrous cartilage.[1708] Whole-thickness skin arthroplasty was performed on seven of the 20 rheumatoid arthritics among 163 patients with 171 arthroplasties of various types; six of the seven patients were "satisfied" with the results.[1611]

Seventeen instances of the use of acrylic prostheses were reported in 14 R.A. patients aged 17 to 77. The patients' evaluation of results, 12 to 60 months postoperatively, was "excellent" in five, "satisfactory" in seven.[1055] However, use of acrylic prostheses was not advised in inflammatory conditions of the hip, including R.A.[537] Rheumatoid arthritis was an infrequent indication for arthroplasty. Of 76 patients who had arthroplasty only four had R.A.,[3396] and only three cup and four prosthesis operations were for rheumatoid arthritis among 43 arthroplasties.[504] [No follow-up studies were reported.—Ed.]

Knee. Synovectomy was advised in all cases with persisting activity in spite of conservative treatment and before pannus formation had destroyed cartilage.[183] [Unfortunately, no data were given to support this advice.—Ed.] Results of 100 arthroplasties with nylon membrane interposition in 86 patients were found two years or more after operation to be excellent in nine, good in 50, fair in 31, and poor in 10. Bony ankylosis from R.A. had been present in 20 knees prior to operation; in 62 other knees there had been extensive destruction of the joint.[2428] One patient with advanced R.A. had the knee joint replaced by a hinged metal prosthesis, with satisfactory results 11 months later.[1961] A hinged acrylic resin prosthesis was inserted in 32 knees of 26 patients with advanced destructive changes from rheumatoid arthritis, some with ankylosis; results were "very good" in 75%.[3209] [Results from these procedures can be assessed only by long-term follow-up studies.—Ed.]

Hands. Methods were described for repair of ruptured tendons, especially the extensors of the fingers, a condition easily overlooked in the rheumatoid hand.[3262] Excision of metacarpal heads and tendon shortening were used to correct flexion deformity and ulnar deviation in one patient.[1202] A replacement arthroplasty for the proximal interphalangeal joint of the finger, using a stainless steel hinge, was applied in 10 instances of ankylosis following trauma, but had not yet been used in other types of joint disease.[374]

Feet. Two patients were subjected to multiple operative procedures on the feet: bevel osteotomy of the plantar aspect of the metatarsal heads was preferred to removal of the heads.[1843]

Jaw. Ankylosis during early years of life produced the characteristic "vogelgesicht" or bird-face; surgical correction was indicated.[2666] A technic for adequate intra-articular injection of the temporomandibular joint was described.[1403] Arthroplasty of the ankylosed temporomandibular joint was described in detail, and yielded satisfactory results in one patient with bilateral rheumatoid involvement of five years' duration.[3203] Correction of ankylosis by creation of an artificial joint with stainless steel onlays was described.[2851] Partial ankylosis of the temporomandibular joint was simulated in one case by bilateral coronoid process exostoses.[3161]

Course and Prognosis in Rheumatoid Arthritis

Further observations were reported on the course of R.A. treated only by hospitalization and "basic regimen," unsupplemented by gold, steroids, phenylbutazone or antimalarials.[415, 838, 839] In a review of a group of 247 of 307 pa-

tients originally hospitalized at the Rheumatic Unit of the Northern General Hospital, Edinburgh, it was apparent that little help in predicting the subsequent course in a patient was obtained from first observations, such as age at onset or disease activity, functional capacity, sedimentation rate and hemoglobin level. Six years following discharge from hospital, only 10% of patients were helpless and dependent upon others. In contrast, 24% were able to perform all normal activities, 40% were moderately incapacitated, and 26% were more severely crippled but not helpless. However, the disease remained moderately active in at least 65% of patients, with no evidence that it had "burned out" even in those most severely disabled. The most favorable prognosis was indicated in patients whose disease ran a progressive course which justified hospitalization within one year after onset of symptoms. Forty-three per cent of patients admitted within the first year were unrestricted in activity six years after discharge, as compared with only 10% of those admitted between the fifth and tenth years. Attention was again called to the fact that two groups were not included in studies such as the above: more mildly afflicted patients not admitted to hospital, and those who never sought medical help. The latter group was estimated to account for 38% of women and 19% of men with R.A.[876]

A method for quantitating the activity of R.A. by consideration of systemic manifestations as well as articular findings was presented in detail and suggested as a subject for further study.[1809, 1810, 1811, 1812, 1813, 1814, 1815] Such systemic and articular indexes proved useful in following the course of the individual patient and in evaluating the results of drug therapy over a three-year period.[1816] A simplified modification of the "systemic index" was proposed.[3208]

Evaluation of therapy in R.A. continued to present many problems. When an "acute" or "specific" drug effect was to be studied, blind and random placebo control had to be applied if variations which resulted from the "treatment situation" were to be excluded.[1296] Long-term use of a placebo, however, was considered to be ethically unjustifiable in a potentially crippling disease.[3208] Problems of therapeutic evaluation were complicated by the highly variable natural course of disease in untreated and conservatively treated patients.

Rheumatoid (Ankylosing) Spondylitis

Incidence and Terminology. Previous definitions were reiterated.[300, 2132] The long-standing confusion of synonyms (ankylosing spondylitis, spondylitis rhizomelique, Marie-Strümpell arthritis, Bechterew's disease, pelvospondylitis ossificans) [1334] [and the unproved implications of etiology they suggest.—Ed] continued. "Histology would support those who would name the disease rheumatoid spondylitis while new serologic findings would oppose this view," [1130] but increasingly, rheumatoid spondylitis was being regarded as not identical with rheumatoid arthritis.[451, 1017, 1352] [The striking difference in sex incidence, the absence of serologic evidence of rheumatoid macroglobulins in the spondylitic, and, above all, the obvious differences in clinical features, natural course and complications, point strongly to a separate and distinct etiology and pathogenesis of these two diseases. It is strongly recommended that these diseases be distinguished clearly and, to avoid unnecessary confusion in future published reports, that they be listed as separate clinical entities.—Ed.]

Connor's original description of an ankylosed spine was reprinted,[302] and an account of his life and works was given.[301] Early writings indicated a relatively

clear understanding of the disease, to which we have added little.[2295] [This reference is an interesting and concise abstract of the literature on rheumatoid spondylitis up to the close of the Nineteenth Century.—Ed.]

Rheumatoid spondylitis was a "fairly common disease,"[2020] but the incidence in the general population was probably little more than 0.1%.[2380] Of 9,852 admissions to a Norwegian hospital for rheumatic diseases during an 11-year period,[1017] 700 were for ankylosing spondylitis, though many patients with mild disease were not hospitalized.[300] Additional studies of incidence were reported.[351, 1334, 2945] "No two series . . . are exactly comparable in all respects."[300] [Opinions differ as to a proper diagnosis in many early cases. See comments concerning prevalence estimates in rheumatic diseases in the Section on General Incidence of Rheumatic Disease.—Ed.]

Family Studies. Familial occurrence of rheumatoid spondylitis or rheumatoid arthritis, or both,[292, 300, 1220, 2939, 3030, 3306] was reported. The pattern of inheritance was that of transmission through a dominant gene:[1220] an estimated six in 10,000 had a "heterozygous genetic constitution for ankylosing spondylitis."[2945] A calculated penetrance of about 70% in men and about 10% in women coincided fairly well with reports of sex incidence in the literature.[2945] However, a peculiarity in families in which women had rheumatoid spondylitis suggested stabilization which made penetrance complete in both men and women.[1220, 2940]

Other Etiologic Factors. Despite recognized genetic factors, the etiology of rheumatoid spondylitis was still "unknown."[1130, 2430] The disease was apparently an inflammatory one,[2132] and possibly one of the "stress" diseases with an endocrine relationship[2989] [a "stress disease" requires definition.—Ed.], or "a nonspecific reaction to diseases of the intestinal tract,"[2957] though amebiasis could not be implicated etiologically.[2661]

Nonspecific urethritis[3030] or gonorrhea preceded symptoms of rheumatoid spondylitis in from 1 to 2%[1334, 3030] to 33% of cases,[812] but treatment for gonorrhea or other infections did not influence the incidence or course of rheumatoid spondylitis;[1130] chronic but largely asymptomatic prostatitis[2007] may have been "part of a systemic mesenchymal disorder."[812] [Reiter's syndrome should be seriously considered in such cases (R.L.B.).—Ed.]

A history of trauma was elicited in 19[1334] to 28.8% of cases.[1852] [This association is often given uncritical acceptance in patients' histories. We do not believe that trauma causes this disease.—Ed.] There was "little or no evidence that climatic or traumatic factors play an important or constant part in etiology."[1352]

Clinical Features. A wide variability, if not inconstancy, in clinical features was recognized.[1702, 2380, 3030, 3306] The onset was acute in 20%,[3306] and occasionally resembled acute rheumatic fever.[1352] Pain frequently was present during only a portion of the course of rheumatoid spondylitis, and was severe in only a third of patients,[300] while symptoms were absent in 4%.[1334] Intermittency of symptoms[1352, 2203, 3085] and frequent back pain at night[1017, 1852, 3306] were stressed. It was "often difficult to decide clinically whether the disease was still active."[2203] In one group the average duration of symptoms was 19 years.[1023]

Ratios of males to females ranged from about 4:1[300, 1017, 2430, 3306] to about 8:1[1198, 1484] to about 12:1.[351] Onset of symptoms before age 15[300, 2007, 3030] or after age 40[300, 351, 1334, 3306] was unusual; average age of onset was between 25 and 30 years.[300, 351, 1334, 2430, 3030, 3306]

Initial symptoms of pain low in the back were reported in 47[1334] to over 60% of the patients;[2430, 3030, 3306] in hip and sciatic regions, in 8,[3306] 16[2430] and 29% of cases;[1334] and in the thoracic region in only 3,[1334] 5[3306] and 9%.[3030] In "the vast majority of patients," symptoms occurred in the distribution of the first and second sacral nerve roots;[3085] "involvement of the cervical region alone was never observed."[2762] [In the adult, involvement confined to the cervical spine is uncommon. In children and in a few adults, obvious physical and x-ray changes are seen in the neck in the presence of acceptable peripheral rheumatoid arthritis; the differentiation of this from rheumatoid spondylitis is not clear at this time.—Ed.]

Initial symptoms indistinguishable from those of "classical peripheral rheumatoid arthritis" occurred in 10 to 22%,[2380, 2430, 3030, 3306] and were "not unusual"[351] in the course of the disease.[300, 1334, 1852, 3030] Deformity of peripheral joint was noted in 12,[1334] 30,[300] and 42% of cases,[1852] and differences between the peripheral joints in spondylitis and rheumatoid arthritis[300, 2132] and unusual sites of involvement[1852, 2380, 2766, 3030, 3306] were described.

Abdominal hernias (predominantly indirect inguinal) in 23%, a finding which "has not been commented on before,"[300] were reported. The second and third cases of rheumatoid spondylitis in prepubertal girls were described.[659, 1959] ["Infantile rheumatoid spondylitis," described by Lucchesi,[1951] was difficult to evaluate in terms of the disease as generally recognized by American or European rheumatologists.—Ed.]

Examination. Maneuvers to determine sacro-iliac involvement were often negative[3085] or inconclusive.[2909] Lower spinal segments were involved more often than upper.[3030] The "chest expansion was nearly always markedly limited";[300] it was two inches or less in 81% of patients with symptoms lasting five years or less,[3306] but was still more than 2½ inches in 25% after illness averaging almost 12 years.[3030]

Subcutaneous nodules did not occur without involvement of peripheral joints,[300, 1017, 1130, 2020] and were found in only one of 54 patients.[3030] [Before any "subcutaneous nodule" in a spondylitic patient could be accepted as a classic rheumatoid necrobiotic granuloma, it would have to be proved by microscopic section.—Ed.]

Clinical evidence of cardiac disease ranged from 1.4 (and was considered to be coincidental)[3306] to 20% of patients.[300] Rheumatic fever either before or after the onset of rheumatoid spondylitis was suspected,[1469] but mitral stenosis did not occur.[2694] [Some of us regard such "rheumatic fever" as transient peripheral joint manifestations of rheumatoid spondylitis.—Ed.]

Pregnancy did not have "the same uniformly favorable influence" on rheumatoid spondylitis as on rheumatoid arthritis,[3306] and the spondylitis rarely became worse after delivery.[1352]

Laboratory Studies. The *blood* showed "no typical changes,"[300, 351] although lymphocytosis[2974] and anemia of varying degrees[300, 1702, 1852, 3306] were reported; average hematocrit readings were "lower than in any form of rheumatic disease."[1130]

Sedimentation Rate was reported as normal in 4,[1130] 18 to 40,[300, 451, 1852] and 76% of cases,[3030] and did not always correlate with symptoms.[300, 1352, 2203, 3306] The rate tended to drop after x-ray therapy.[1702]

Tests for *rheumatoid factor* were "rarely positive."[159, 300, 1017, 1130, 1352, 2020, 2313, 2515, 2789, 3306] In 16 postpubertal spondylitics with rheumatoid arthritis of juvenile onset, results of "sensitized sheep cell agglutination tests resembled those obtained

in adult peripheral rheumatoid arthritis rather than those in adult ankylosing [rheumatoid] spondylitis."[3417]

Serum *electrophoresis* showed increased gamma and alpha$_2$ globulins;[1130] serum glycoprotein and the ratio of bound carbohydrate to protein were also increased.[1959, 2786] Correlation coefficients between diphenylamine and nonglucosamine polysaccharide levels were "highly significant."[12] Values for urinary glucuronide did not differ significantly from those of a control group;[1472] neither did plasma 17-hydroxycorticoid levels at different intervals during the day.[3225]

The *C-reactive* protein was positive in eight of nine patients without involvement of peripheral joints,[2786] but the antistreptolysin titer was rarely elevated.[159, 2786] *Cerebrospinal fluid* protein was increased in five of 20 cases.[300]

Roentgen Features. Bilateral sacro-iliac arthritis was still the most important and consistent finding in virtually all patients.[351, 3030, 3085] Evolution of sacro-iliac changes extended from a few to 20 years,[3085] and averaged 14 years to ankylosis, but this did not necessarily imply that the disease was arrested.[1023] Ankylosis sometimes developed without other features of rheumatoid spondylitis.[1017, 3085]

Bilateral changes in the sacro-iliac joints needed to be differentiated from osteitis condensans ilii,[451] other "syndromes of pelvospondylitis,"[3085] and "atypical spondylitis."[2762] [These entities need further elaboration and more common acceptance of diagnostic criteria.—Ed.] The roentgenologic pattern in female patients was considered to be different from that in men. The predominant female pattern was: (a) marked involvement of the posterior spinal articulations; (b) little or no ligamentous ossification; (c) osteoporosis, and (d) considerable calcification of costal cartilages.[2132] [This study requires confirmation.—Ed.]

Vertebral Column. Sequential changes leading to ossification[1749] and vertebral erosions or sclerosis ("anterior spondylitis") were described,[3306] but only 16% of patients had the "typical bamboo spine."[3030] Osteoporosis of the spine was found in 24[1852] to 30% of cases.[300]

Extraspinal Features. Involvement of the hip joints was found radiographically in 15%;[1852] it was unilateral in 7% and bilateral in 9% of cases.[3030] A "whiskery" bony proliferation of the exterior aspects of the pelvis, upper parts of femora, and feet at the site of muscle attachments was "quite characteristic"[3030] and frequent.[2132, 3306] [These various manifestations of osteopathy, extraspinal as well as spinal, are an integral part of this disease, as are the lesions involving synchondroses such as the symphysis pubis, manubriosternum and intervertebral disc. —Ed.] Involvement of the symphysis pubis[2132, 3030] closely resembled (histologically as well as radiographically) changes in the manubriosternal joint.[696] Generalized osteoporosis was usually absent in peripheral joints; destruction of articular cortex differed from that of rheumatoid arthritis in progressing away from the articular cartilage.[2132]

Pathology. "For a disease which is by no means uncommon, there is a remarkable lack of hard pathological data."[300, 1130] The disease began as villous synovitis, like that of rheumatoid arthritis, but its course was more rapid.[1130] The amount of sacro-iliac synovial tissue was small in comparison with the surface area of the joint; thus, subchondral lesions were of greater importance.[696] Variable innervation accounted for different sites of referred pain from sacro-iliac joints.[2909]

Spine. Bone was destroyed at the junction of cortex and connective tissue,[2132] and ossification was "accelerated,"[740] but calcified ligaments were "entirely inexplicable."[2020] Ossifications of the lateral region of the disc accounted for the roentgenographic appearance of the bamboo spine.[696] Intervertebral discs were ossified in 38, loose fibrous tissue replaced the nucleus pulposus and annulus in six, and discs were normal in 17 cases.[696]

In "older cases" subjected to lumbar osteotomy, extensive adhesive arachnoiditis[2430] with fibrous and bony proliferation encroached on the foramina.[2090]

Other Joints. Histologic synovial changes were identical,[1130] but information concerning pathology of the articular lesion of rheumatoid arthritis and rheumatoid spondylitis was still based on a small number of cases.[300] Symphysis pubis and manubriosternal articulations showed a similar sequence of pathologic changes.[696]

Heart. "The typical lesion of the aortic valve and ascending aorta" grossly resembled syphilitic aortitis[2020] but was less diffuse.[1218] All layers of the aorta were involved,[93, 2694] but the mitral valve was not, and no Aschoff bodies or rheumatoid granulomas were found.[1218, 2694] At necropsy, the posterior wall of an aorta was firmly adherent to the adjacent anterior longitudinal ligament; no previous references to this condition were found.[1890] [X-ray therapy had been given.—Ed.]

Other. A case of renal amyloidosis in a spondylitic was described, but "the association . . . must be rare."[1299] [One of us (D.C.G.) has observed two such patients in the last two years.—Ed.] Spindle-shaped collagenous structures in gastrocnemius muscle fibers of six of 17 patients with rheumatoid spondylitis could not be found in patients with rheumatoid arthritis or other diseases.[3119] [This has not been confirmed.—Ed.]

Diagnosis. It was "surprising that so distinctive a disease was not generally recognized sooner,"[451] but "the time from the earliest symptoms until a definitive diagnosis [could] be made [was] a varied period beset by many difficulties, both for the patient and the physician."[1334] The interval varied from less than one year in 44% to more than 10 years in 9%;[3030] the average interval was 44 months.[1334]

Differential Diagnosis. This required consideration of many spinal diseases,[451, 2707, 2909] including rheumatoid arthritis of the spine.[2762] [There was no indication of the way this was done.—Ed.] Rheumatic fever, Reiter's disease and psoriasis with spondylitic involvement also were differentiated, "although most of them had bilateral radiographic changes in the sacro-iliac joints."[2762] [This was also discussed in the Twelfth Rheumatism Review.—Ed.] The principal points of differentiation between osteitis condensans ilii and ankylosing spondylitis were listed.[3085]

General Therapy. Conservative treatment was "definitely helpful for most patients."[3030] Physical therapy appeared to be more efficacious in maintaining function than did prolonged rest in bed with casts;[300, 1352, 2490] therapeutic exercise[300] was one of the "notable advances" in "the last 25 years."[2762] Ultrasonic therapy[1341, 3074] and an active rather than a sedentary occupation were advised.[1352] A spondylometer to record progress was an "invaluable aid."[3079] Prevention of deformity was "misdirected" if it resulted in the patient's not being able to sit.[451, 1352]

Roentgen Therapy, Including Hazards. X-ray therapy remained a commonly used treatment,[300] but it needed to be combined with other measures.[1484, 1702, 3306] Reported results generally agreed,[300, 1353, 1484, 1702, 1852, 2203, 2399, 3306] but only two of 52 patients had some roentgenographic evidence of improvement.[1702] [Not described, and we doubt that any ever occurs.—Ed.]

Modus Operandi. This remained unknown,[1702] but several concepts were proposed.[1130, 2766] Relief of symptoms from adrenal irradiation was "confirmed."[2898] [Any implication that roentgen radiation produced therapeutic effects by its action on the adrenals requires more evidence before it can be accepted.—Ed.] Progressive ligamentous calcification was not prevented,[2430] and whether the disease was arrested "more than temporarily"[3306] was still "a debatable question."[1702]

Dosage. Diversity in dosage produced remarkably uniform results.[2989] Since 1956, lower doses (1,200 to 1,800 r) have been used,[1484, 1702, 2377, 2979] or only symptomatic areas have been treated, and multiple courses "eschewed."[3306]

Dangers of X-Ray Therapy. Serious complications were "rare,"[2766] but x-ray therapy more nearly approached whole-body irradiation than that given for any other nonmalignant condition.[1484] Leukocytes were depressed in the immediate postirradiation period;[1198, 1702, 2203] *bone marrow* (during study of effects of roentgen therapy) was hyperplastic in 39[2399] to 43%,[2974] with hypoplasia or aplasia later.[2974] Secondary anemia, aplastic anemia,[1198, 2762] activation of and hemorrhage from duodenal ulcer, alteration of menses[1484] and breakdown of quiescent pulmonary tuberculosis[141, 3306] were among complications reported.

Although "the dangers of affecting the skin and marrow are practically nil,"[1702] [a dangerous and unconfirmed assumption.—Ed.] estimates of marrow absorption were necessarily approximate,[662] and regeneration was still incomplete 15 months to 14 years after x-ray therapy.[2974] It was "concluded that irradiation plays the main part in the production of the observed cases of leukemia,"[4] although additional factors in selection were noted.[4, 76, 1484] The risk of leukemia was one in 225, in comparison with one in 2,000 in 10 years,[1484] and mortality was about 10 times greater than in a normal population of the same age and sex distribution.[76, 662] Twenty-eight fatalities and three patients alive with leukemia were found among 13,352 spondylitics given x-ray therapy in 81 centers in England between 1935 and 1954.[662] [In Canada and the United States, deaths from leukemia in irradiated spondylitis have been reported as follows: of 146 patients, there were five with leukemia; in a control group of 445 nonirradiated spondylitics, there were no cases (Silberberg, D. H., Frohman, L. A., and Duff, I. F.: Arthritis and Rheumat. **3**: 64 [Feb.] 1960). In a second group of 496 patients, there were five deaths from leukemia; a control group was not available (Graham, D. C.: Arch. Int. Med. **105**: 51 [Jan.] 1960). The cause of death in an English series of 419 irradiated spondylitics included 10% due to leukemia and 18% due to malignant tumors (Cruickshank, B.: Bull. Rheumat. Dis. **10**: 209 [Feb.] 1960).—Ed.] No cases of leukemia were found in Blumberg's series;[300] only one was recognized with certainty in a woman.[662] The incidence of leukemia increased with the age of the patient at the time of irradiation,[662, 2176] but there was no threshold dose.[662, 663]

"Some reorientation of our attitude" toward liberal use of x-ray therapy was advised.[3085, 3306] [Leukemia among x-ray-treated spondylitics has been reported in the United States; most of us have become more conservative in the use of x-ray therapy. Some of us have discontinued its use. Since the chief effect of this agent is analgesia, it would seem unwise at the present time to risk the development of leukemia by its continued use unless all other forms of symptomatic treatment have failed,

and the patient and the physician mutually accept the possibility of this increased hazard.—Ed.]

ACTH and Steroids. Steroid therapy presented problems "as difficult as the problems of [its] use in any other disease,"[2380] but it was preferable to radiotherapy "when child-bearing is likely," and when used for a short period.[1017, 1072] Although ACTH or adrenocortical steroids were "more effective" than roentgen therapy,[451] they were "usually not necessary";[300] "their great use" was for "the frequent, complicating iritis."[451] [The general plan for systemic steroid therapy is the same as that for rheumatoid arthritis, and is usually reserved for patients with peripheral joint disease.—Ed.]

Phenylbutazone. Phenylbutazone was generally beneficial along with other treatment,[300, 2380, 2430] and was effective in a higher percentage of spondylitics than in patients with peripheral rheumatoid arthritis.[1221, 1788, 2010, 2020, 3113] When childbearing was likely, phenylbutazone in small doses was preferable to radiotherapy.[1702, 2010] [No data were presented to support this conclusion.—Ed.]

Improvement was expected within seven days,[1221] and was based largely upon subjective response,[1313] but many patients showed improved mobility of the neck and chest expansion.[3113] In 50% of those with good subjective response, use of phenylbutazone had to be discontinued because of toxicity.[3030] [This is an unusually high complication rate.—Ed.] Oxyphenylbutazone, a derivative of phenylbutazone, was beneficial in two patients, including one with iritis.[2321] [This is a preliminary report.—Ed.]

Surgery and Other Therapy. Surgery had "only a limited usefulness,"[300, 451, 1352] especially if hips were involved.[2185] Lumbar osteotomy,[1890, 2917] preferably called "posterior elementectomy,"[740] was successful in a 17 year old girl,[659] but was contraindicated by deformity of the hips in addition to kyphosis;[2090] prolonged postoperative spinal support was needed to prevent recurrence.[2090] Correction of a severe cervical flexion deformity[3149] and spontaneous atlanto-axial dislocation[2764] was reported. [Spontaneous atlanto-axial subluxation is a more common complication than is generally realized.—Ed.]

Other. "Effective relief" was reported in 15 of 16 patients (93.7%) given zoxazolamine,[2871] and in 19 of 21 patients (90%) given meprobamate.[2870] Iproniazid therapy caused symptoms to "routinely regress."[353] [No details were given.—Ed.]

Course and Prognosis. Rheumatoid spondylitis had a variable course,[300, 451, 1334, 1890, 2132, 2430, 3306] with relapses in 43% of cases.[1484] "After 10 years of illness, most spondylitics [were] reduced to sedentary or light occupations," [we do not agree.—Ed.] but extraspinal joint lesions were "unlikely if they had not already occurred."[3306] The spinal column remained mobile to some extent in 54[1334] to 88%[3306] of patients after 10 years of symptoms; complete ankylosis had occurred in 12[3306] to 29%; recovery with no stigmata whatsoever occurred in only 1%.[2430] Involvement of the hip was an unfavorable prognostic sign.[3030]

Socio-economic Factors. Sixty per cent of patients,[1484] or more,[300] "could earn a living"[2203] or "were working full time,"[1353] but the percentage decreased with increasing duration of disease.[300, 3306] Those self-employed or able to obtain midday rest were best adapted to the limitations of the disease.[3030] [See also Rehabilitation in Rheumatic Diseases.—Ed.]

Complications. Iritis occurred in from 10 to 25%[1017, 1353, 2380, 3306] or more[2309] of cases. [Prevalence of uveitis increases distinctly with increasing duration of dis-

ease. This might explain many of these differences in observation regarding its prevalence.—Ed.] Involvement of the iris and ciliary body only was peculiar to those patients with roentgenographic evidence of ankylosing (rheumatoid) spondylitis.[2931]

Tuberculosis and Other Pulmonary Complications. Pulmonary tuberculosis occurred twice [1841] to 20 [1484] times as often as was anticipated statistically in English cases, but was not related to roentgen therapy.[4] In one American study it was reported in two of 23 patients treated with phenylbutazone,[1788] but in other American series there was a "paucity of pulmonary complications." [300, 3030]

The incidence of *malignancy,* excluding leukemia, was no greater than expected.[4, 1484, 2203, 3306]

Cardiac Disease was noted in 7 [3306] to 13% [3030] of cases, but caused death in about 15% in another series.[300] A study made in a large American hospital found the aortic valve involved in 15 spondylitics in a 10-year period (all cases but one authenticated at necropsy were in males); [2020] it was involved in five of 25 patients with "rheumatic fever" before or after onset of rheumatoid spondylitis,[1468] but in less than 5% of a Canadian war veteran series.[1218] Rheumatoid spondylitis was present in five of 100 patients with aortic insufficiency.[2694] "The 50% survival time after onset of free regurgitation was seven years," and the incidence of aortic insufficiency rose from 3.5% after 15 years of rheumatoid spondylitis to 10.1% after 30 years.[1218]

Other Complications. Peptic ulcer occurred in 3 [3030] to 6% [3306] of males; 12 [3306] to 25% [1353] had significant dyspepsia. Chronic ulcerative colitis [3306] or regional enteritis, or both,[2957] psoriasis,[1334, 3030, 3306] hemorrhagic diathesis due to an acquired circulating thromboplastin inhibitor,[812] rheumatic fever and rheumatoid arthritis,[1334, 3306] [the peripheral joint manifestations of rheumatoid spondylitis?—Ed.] and herniated intervertebral discs [1334] [proof not stated; this is not common in spondylitics.—Ed.] were reported; so were spontaneous atlanto-axial dislocation in 10 advanced cases,[2764] and paraplegia from a fracture of the cervical vertebrae.[3030]

Osteoarthritis (Degenerative Joint Disease)

Definition. Little was added to restatements of accepted basic concepts of osteoarthritis outlined in previous Rheumatism Reviews.[411, 433, 526, 919, 1021, 2637, 2946, 3017, 3118, 3196] The terms "osteoarthritis," "degenerative joint disease," "hypertrophic arthritis" and "osteoarthrosis, including spondylosis" continued to be used interchangeably. The majority of authors adopted the distinctions of "primary" and "secondary" changes, with emphasis usually placed on primary osteoarthritis. Stecher was of the opinion that osteoarthritis represented a group of related but different specific diseases.[2946] He challenged Kellgren's concept of generalized osteoarthritis. [This condition was summarized in the Eleventh Rheumatism Review.[1k] Few references have appeared in the eight years since the original publication. We find this a difficult entity to diagnose. The clinical course closely simulates R.A., but the serologic test for R.A. is negative. One of us (R.W.B.) believes that this entity exists but, for the rest of us, its existence as a separate entity remains to be clarified.—Ed.]

Incidence. Osteoarthritis increased with advancing age, occurring in 80 to 95% of the population beyond the fifth decade, but causing symptoms in only 5 to 10%.[317, 411, 526, 593, 1506, 1915, 2281, 2360, 2637, 2945, 2946, 3118, 3139, 3180, 3197] In Birm-

ingham, England, 1,062 men in the seventh decade were examined and 69 (6.5%) were found to have osteoarthritis.[416] Sites of involvement showed some differences in sex, although the over-all incidence was the same in both sexes.[411, 433, 3118] Women with Heberden's nodes outnumbered men 10:1.[433, 2939] In a New York industrial population of 28,000, osteoarthritis occurred in 14% of patients, and was more frequent than gout and rheumatoid arthritis combined; it was exceeded in prevalence only by bursitis.[433] Involvement was of the spine in 75%, of the knees in 25%, of the hips in 7%, and of other joints in 5%. Women with degenerative joint disease experienced symptoms more often than did men.[433] About 10% of osteoarthritis patients had symptoms referable to the cervical area.[1926] Involvement of the sternoclavicular joint was more common than is generally appreciated.[103] The temporomandibular joint was involved in 3% of 256 patients.[2708] Of 556 consecutive cases referred to a physical therapy unit, 28% were referred for treatment of osteoarthritis; only 10% were referred to this same unit for postoperative and traumatic conditions.[2006]

Clinical Aspects. The evolution was concisely summarized by Marian Ropes: "Histologic alterations at 20, radiologic changes at 40, and symptoms at 60." [2637] But only 5 to 10% of those with pathologic changes showed symptoms. [The role of personality factors and pain threshold received surprisingly little attention.—Ed.] Onset was frequently acute following injury, but as a rule the onset of the cardinal symptoms of pain and stiffness was insidious, with gradual development of deformity and disability; at times, clinical features were at striking variance with pathologic data.[3196]

Causes of Symptoms. There was general agreement that most symptoms were related to pain-sensitive soft tissues in and about the involved joint, and not to the joint itself.[411, 433, 734, 1401, 1461, 3118, 3197] Other sources of pain discussed were: (1) reactive changes in subchondral bone in relation to deep and diffuse aching pain, possibly caused by increased vascular engorgement of the head of the femur;[734, 3197] (2) synovitis with capsular fibrosis and shortening and limitation of motion;[433, 734] (3) increased joint temperature in symptomatic osteoarthritis following exercise,[1461] and (4) disruption of venous return with engorgement of cancellous bone.[1499] In response to a questionnaire, 48 practicing orthopedic surgeons and 96 rheumatologists expressed their opinions regarding relationship of injury to the level of symptoms in patients with degenerative joint disease.[2793] Eighty-two per cent of the rheumatologists and 88% of the orthopedic surgeons stated that it was "probable" rather than "possible" or "improbable" that a person with previously demonstrable changes, yet without symptoms, could be rendered symptomatic by a single acute trauma.

Special Locations. Heberden's nodes were a local manifestation of osteoarthritis, despite their peculiarities,[196, 411, 919, 1668, 3118] or were a process distinct from generalized osteoarthrosis and unassociated with severe generalized joint involvement.[2945] A striking resemblance to acromegalic tufting of the phalanges was reported.[3118] "Traumatic Heberden's node" was a distinct secondary process occurring after the seventh decade in 30% of the women but in only 3% of men. Males were affected only as homozygous, females as heterozygous, carriers of the sex trait.[2945]

The relation of Heberden's nodes to the menopause was reiterated.[2945] Symptoms were again noted to be variable: pain, tenderness, and effusion might or might not occur during their development, and deformity was common.[411] The

proximal interphalangeal and wrist joints were usually unaffected.[919] [Nevertheless, isolated or associated involvement of proximal interphalangeal joints occurs often enough to be confusing. Changes in these joints (Bouchard's nodes) frequently present features which may be mistaken for rheumatoid arthritis.—Ed.]

Temporomandibular Joint. The incidence of osteoarthritis was about 3% in 256 patients with painful temporomandibular joints.[2708] Among 28 symptomatic patients, the average age of onset of symptoms was 35 years.[470] Roentgenograms were frequently of limited diagnostic value.[1044]

Shoulder. Osteoarthritis in the glenohumeral joint was rare but did occur, chiefly after trauma.[1021]

Knee. The knee was found to be one of the most frequent sites of osteoarthritis.[411, 443] Obesity was commonly associated.[1654] In 39 patients, genu varum occurred in 33%, lateral instability in 75%, and "suprapatellar adhesions" in 25%. Recurrent synovitis of the knee was considered to be an early sign of osteoarthritis, and "if the synovitis persisted for more than three months the knee should be explored."[1048] Osteoarthritis associated with juxta-articular painful fat pads over the medial aspect of the knees (Hoffa's disease) in a Hindu female was reported.[2966]

Hip. Osteoarthritis in this joint was again described as the most disabling form of degenerative change.[411]

Pathology. Comprehensive discussions were presented.[433, 524] Trueta re-emphasized the increase in vascularity of bone in osteoarthritis, and stated that the primary initiating factor in degenerative changes of cartilage depended upon the distribution of intra-articular pressures.[3127] Pathologic alterations in any given joint seemed to be independent of those in any other articulation, or of systemic influences.[614] Disruption of the venous plexus in osteoarthritis of the hip was demonstrated.[1499] Electron microscopy showed normal cartilage to consist of a three-dimensional, nonoriented collagen fibrillar network, while that in osteoarthritis had definite orientation of fibrils.[1910]

Etiology and Pathogenesis. *Microtrauma.* Trauma in various forms was universally held to be a major contributory factor, although not one of the initiators of the symptomatic degenerative process.[526, 734, 919, 1459, 1896]

Hormonal Factors were considered to be contributory, but there was vagueness regarding the relationship. The menopause was important,[433, 1459, 2946] and significant associations were reported with acromegaly and Cushing's syndrome,[1459] decreased production of steroid hormones,[3139] thyroid deficiency and obesity.[433] [Long-range, analytic and controlled clinical observations in this area, especially in relation to the menopause, are needed.—Ed.]

Heredity. The hereditary aspects of Heberden's nodes were widely acknowledged.[367, 433, 919, 1459, 2945] The influence of heredity on other sites of involvement, however, was indefinite.[433] A familial tendency toward premature osteoarthritis was noted.[919]

Laboratory Data. The noninflammatory nature of the synovial fluid was emphasized.[411, 1459, 3118] The erythrocyte sedimentation rate (E.S.R.) was found to be moderately elevated in about 40% of patients.[411] [The ESA is not elevated due to osteoarthritis. We do not know how the frequency of elevated ESRs in patients with osteoarthritis compares with a closely comparable population sample of people with no apparent disease.—Ed.] A variety of laboratory tests and examinations failed to reflect systemic inflammation.[433, 919, 1459, 3118] Punch biopsy was used to

study the synovialis.[411, 1459] Urinary gonadotropin excretion was normal.[2578] The gelatinous fluid from Heberden's nodes was shown to contain free hyaluronic acid.[1533] In affected knee joints, noises during motion were recorded.[1502]

Roentgen Studies. The radiologic minutiae of osteoarthritis were fully described,[2916] and the great lack of correlation between radiologic appearance and symptomatology was emphasized.[18, 397, 411, 433, 526, 593, 1774, 2281, 2916, 2946, 3139] Criteria for grading degenerative joint disease according to radiologic features were presented.[1669] Detritus cysts were difficult to distinguish roentgenologically from punched-out lesions of gout or rheumatoid arthritis.[411]

Treatment. *Medical.* The basic measures of medical therapy continued to be reassurance, rest, supports, exercise, heat, weight reduction and time.[411, 433, 526, 919, 1463, 1915, 3118, 3140, 3197] To these were added analgesics, with salicylates leading the list, followed by phenylbutazone. Caution regarding the toxicity of phenylbutazone was universally advised. The use of steroids on a systemic basis was discouraged.[2750] [The majority of us consider that the use of oral adrenocortical steroids in degenerative joint disease is without justification. The hazards far outweigh any possible benefit. Two of us (M.M.M. and O.S.) use them at times in severe osteoarthritics with "acute" symptoms.—Ed.]

Local intra-articular injections were advocated for temporary relief of pain,[411, 433, 526, 919, 1463, 1817, 1867, 1915, 2616, 2750, 3118, 3140, 3176, 3197, 3426] even in the temporomandibular joint.[658]

The experience of a Scottish group showed results contrary to those reported by most other observers.[2156] This was a well designed and conducted control study, using solutions of lactate plus Novocain, Novocain-saline, hydrocortisone and a mock injection. The five forms of injections were made into the knee on five occasions at two-week intervals. Six weeks after cessation of treatment, the patient's opinion and an objective assessment were recorded. There was no significant difference in the effect of the three therapeutic agents investigated. Furthermore, the benefit which resulted from the saline and mock injections was just as great as that from the three active solutions. [This stringently controlled clinical trial casts doubt upon the value of this popular form of treatment in this disease. In contrast to this view, we believe that many patients with active synovitis secondary to degenerative joint changes are benefited for short periods by intra-articular corticosteroid therapy. However, repeated therapy of this type in weight-bearing joints may, as a result of pain relief, be used more. The increased trauma of use will contribute to a more rapid progression of osteoarthritis and more irreversible joint changes.—Ed.] Narcotics other than codeine were not advised, except in one instance.[3140] [All forms of narcotics are to be avoided, except that in exceptional instances, and for unusually painful, acute episodes, codeine may be used.—Ed.] The results six months after repeated intra-articular injections of benzyl salicylate in oil into the knee joints of 53 patients were "encouraging," and justified further investigation.[2612]

Colchicine, cinchophen, iodides, snake venom, liver extract, vaccines, gold salts, oral procaine and antibiotics were considered to be ineffective.[433, 1782, 2105] Therapeutic benefits were also claimed for hesperidin-methylene-carboxy-chalcone;[2358] zoxazolamine (Flexin);[2871] a combination of calcium aspirin, calcium succinate and suprarenal cortex;[3304] phenylbutazone and compound F;[3002] an endocrine mixture consisting of estrogens, androgens and thyroid extract;[1395] a tranquilizing agent, perphenazine;[2746] and an analogue of phenylbutazone (oxy-

phenylbutazone). [Most of these reports contained the all too frequent favorable comment based upon poorly planned clinical trials, without objective criteria of change and with no control observation. This type of unreliable reporting continues to flood certain medical journals and clog this important channel of communication. Although such uncritical reports are becoming less common, they continue to appear, and cast reflection on the judgment of the editors of these medical journals. Products of dubious value are far too frequently promoted by the manufacturing company, and the cost, as always, is borne by the unsuspecting patient.—Ed.]

Physical Therapy. Physical therapy and corrective exercises continued to be universally advocated, but no significant advance in this area has been made since the last Rheumatism Review. Favorable results of ultrasound therapy were reported.[1058, 2004, 2177, 2288, 3074] [The reports appear to be too laudatory. Evaluation of this modality remains to be clarified by objective, well designed and carefully controlled studies.—Ed.] Manipulation of painful osteoarthritic joints following injections of lactic acid was described.[2111] [Evidence to support the claims was inadequate.—Ed.]

Surgical. Surgery was the last resort for intractable pain and disability in osteoarthritis of the hip and knee joint unresponsive to medical therapy.[126, 196, 411, 1709, 2152, 3210] [This aspect of treatment is being pursued in experimental research; future results may offer more promise.—Ed.]

Knee. Nylon arthroplasties were fairly successful in restoring painless motion at the knee;[126, 411, 1709, 2428, 3210] of 32 patients, 75% derived freedom from pain and complete steadiness with an acrylic resin prosthesis.[3210] Brown and co-workers reported the use of skin as an interposing membrane for knee arthroplasty in four patients, and found that it held up well.[414] Patellectomy for degenerative joint disease in 109 patients followed for from two to seven years gave symptomatic improvement in 83 patients, and freedom from pain in 47.[1300] [No really satisfactory prosthetic replacement device for corrective surgery of the knee is yet available, though progress is being made.—Ed.] Another report, based upon a more limited experience, was also favorable.[752] Pain was also decreased by thorough local debridement.[2152]

Hip. Various indications and contraindications and types of surgery were advocated and criticized. No single procedure, prosthesis or approach was without sound adherents or severe critics.[8, 125, 126, 196, 537, 751, 1709, 2146, 2981, 3150, 3239] Arthrodesis for unilateral hip disease was vigorously defended by Watson-Jones, who obtained sound bone fusion in 94% without any mortality in 120 patients.[3239] Vitallium cup arthroplasty gave good to excellent results in 22% of osteoarthritic hips.[126] Over-all satisfactory results in hip replacement arthroplasty were in the 40 to 86% range, with a wide variety of indications, approaches and devices used.[125, 504, 537, 1611, 1613, 1907, 2981, 3127] Osteotomy continued to be advocated and defended.[11, 143, 2146] [To a great extent, the marked variations in statistical observation and selection of cases reflect the differences in criteria for evaluation of results. Much work is needed to improve surgical technics and to discover means of choosing those who might benefit and those who might not be helped, or might even be made worse.—Ed.]

Other Surgical Procedures. Extended lumbar sympathectomy gave lasting relief of pain in seven patients.[1413] [In a personal communication to one of us (O.S.), this author reported having done this operation on 64 patients in the last five years. In 60% of these he considered the results as "good." Twenty patients are now in the third postoperative year, and "nearly every one of these reported good relief of

pain." Fifteen patients with osteoarthritis and R.A. treated by this surgical procedure and followed for four years were reported by this group in 1959 (Arch. Phys. Med. **40**: 133 [Apr.] 1959). These claims have been reported from only one hospital. Their results are unusually and uniformly favorable in studies extending over a six-year period. If others have tried this procedure, we are unable to find any published account of their results. The opinions of some additional observers would be most welcome.—Ed.] Obturator neurotomy gave good results in 60% of 50 patients.[3282] [Caution in accepting this report without further support is urged.—Ed.] Skin arthroplasty compared favorably with other forms of arthroplasty, with about 65% "satisfactory" results.[1611] Resection of the outer one-half inch of the clavicle usually gave prompt and gratifying relief of pain; arthrodesis of the acromioclavicular joint was not recommended.[2954] In another study, acromionectomy was preferred.[1222]

Roentgen Therapy. "Fair results" were observed in some patients and were related to the dose.[1702] Kersley treated 429 patients according to a three-dosage plan, with the total amount of radiation depending upon the size of the joint. For example, the low, medium and high dosages for a knee or ankle were 500 r, 750 r, and 1,000 r, respectively. Of 102 patients who received the largest dose, 59 were "improved" and 41 showed "marked improvement" in degree of pain. [We do not agree, and find no place for roentgen therapy in degenerative joint disease. The x-ray apparatus is a potent psychotherapeutic agent but, despite this, roentgen therapy has not gained in favor.—Ed.]

Osteoarthritis of the Spine

Incidence and Etiology. The incidence of osteoarthritis of the spine was found to parallel and even to exceed that of other joints. In one survey the incidence was reported as follows: "The site of involvement which gave rise to symptoms was in order of descending frequency, spine 73%, knees 25%, hips 7% and other joints 5%."[433] Cervical osteoarthritis was encountered in at least 10% of patients suffering from osteoarthritis.[1775] The frequency increased directly with age.[1506, 1774] The etiology was commonly thought to be related to wear and tear of the discs and the ligamentous structures, provoked primarily by the microtrauma of living.[254, 366, 705, 790, 1749, 1774, 2723] Distinction was often made between osteoarthritis of the true synovial joints of the spine and disc degeneration with spondylosis[2360] [a distinction to be encouraged.—Ed.]. The existence of joints of Luschka as true synovial articulations was affirmed[343, 1774] and denied.[2360, 2529] They were, nevertheless, frequent and important sites of bony proliferation.[343]

Symptoms. The discrepancy between symptoms and radiologic findings was reëmphasized.[366, 901, 1562] Symptoms were ascribed to the stretching of muscles and ligaments over osteophytes, and pressure on nerve roots, the spinal cord and sympathetic nerves.[1775] [The mode of symptom production remains obscure in the majority of cases.—Ed.] Progressive dysfunction of the spinal cord, with varying signs and symptoms of quadriplegia, was noted in cervical spondylosis, as were hoarseness and painful deglutition.[366, 371, 922, 1386, 2723, 3053] Brain and Wilkinson collected 17 cases with disseminated sclerosis and cervical spondylosis, noting the diagnostic difficulty.[371] Brachialgia, radicular or diffuse, was present in 33% of 78 patients presenting cervical spondylosis with neurologic deficit.[366] Compression of cervical nerves in the foramina was attributed primarily to osteo-

phytosis at the joints of Luschka.[343] [Selective degenerative lesions were emphasized by individual authors according to their special material or viewpoint, but the consensus of observations indicated that provocative lesions may arise from any of the margins of the joints and osseous components of each foramen and the pathologic changes mentioned in the next paragraph.—Ed.]

Pathology. The pathology of osteoarthritis of the spine arising from its articulations was imputed largely to degenerative changes at two of its structures —the intervertebral joints, and the uncovertebral articulations or joints of Luschka. The alterations were accepted by most authors as similar to those at joints elsewhere in the body,[272] osteophytosis, subluxation with or without joint space narrowing, and in association with disc degeneration.[254, 343, 366, 705, 790, 1749, 1774, 2360, 2723] The pathologic proliferation of bone was similar, even when the initiating stimulus to degeneration differed at these sites. Actual herniation of the disc as an originating factor in the pathology was both disputed[1775] and affirmed.[366] The role of disc degeneration was similarly controverted.[366, 705, 1749, 1774, 2723] Fibrosis of nerve root cuffs was described as another factor responsible for symptoms.[2264]

Roentgen Studies. These provided the basis for observations on the incidence and relationship of symptoms to pathology. As already stated, little correlation was found between findings and symptoms.[18, 366, 1506] The roentgenographic changes of the border of the vertebral body which distinguish osteoarthritis from degeneration of the disc, ankylosing spondylitis and epiphysitis were presented.[1749] The importance of oblique views of the cervical spine for adequate visualization of the joints of Luschka and the foramina was stressed.[343, 790, 983, 999, 1030] Myelography, especially in the presence of spinal cord symptoms, was emphasized as a valuable diagnostic aid.[366] [This procedure is never used except when surgery is imminent, and then only to confirm location of a disc (E.F.R.).—Ed.]

Treatment. Most of the papers dealt with cervical spondylosis. In the absence of neurologic deficit, conservative treatment, consisting of cervical collars, traction, local heat, diathermy and other radiant therapy, as well as analgesics, was advised.[427, 1030, 1774, 1775, 2723] Kuhns estimated that surgery was necessary in 10% of patients.[1774] In the presence of neurologic deficit, the number of compression sites influenced the results of medical measures. Results were reported to be fair with one compression point, but poor with two or more.[366, 2723] Surgery consisted of laminectomy with sectioning of the dentate ligament; the mortality rate was 10% in 31 patients. The initial results, as judged by walking, were satisfactory; sphincter control was improved, but within six to 18 months, 50% began to deteriorate.[366] [Evidently, surgery in this area requires unusually compelling circumstances, and is advised only in selected cases. —Ed.] Few papers gave adequate statistics concerning the results of surgical or other treatment. A new anterior approach for the removal of cervical discs combined with fusion of vertebrae was described.[2858]

Ultrasonic radiation was administered to 119 patients with osteoarthritis involving the cervical, dorsal and lumbar areas, with "relief" in 96%.[2524] [Other measures of therapy included "manipulations" and vertical traction. No objective data reflecting improvement were present.—Ed.]

Part II

Backache and Sciatica

Prolapse of the nucleus pulposus or protrusion of an intervertebral disc was still considered to be the most frequent cause of low back pain or backache, but there were fewer papers on the disc problem. Other mechanical causes of low back pain were listed or briefly discussed, but with little new information. The general subject of backache, symptoms, physical findings, diagnosis, and principles of treatment was reviewed in many papers.[520, 558, 624, 1126, 1184, 1242, 1247, 1387, 1440, 1546, 1612, 1827, 2068, 2114, 2269, 2325, 2352, 2356, 2596, 2994, 3334]

The old-fashioned term "lumbago" was used more frequently, and was defined as pain in the low back, abrupt in onset, severe and crippling, but of short duration. It was attributed to trauma, often with injury to muscle or ligaments, and not necessarily to disc protrusion.[453, 619, 2994] Investigation of low back pain complaints by "functional radiography" added little to information obtained by routine radiography.[25]

The nerve supply to structures of the back and radiation of pain from various lesions were reviewed,[2960] as were the segmental neuralgia syndromes.[1546] Origins and terminations of nerves to the vertebral column and its associated structures were found, in the monkey as in man, to furnish a one-segment overlap in the spine and in muscles, corresponding to a similar cutaneous dermatone overlap. Nerve terminations considered to be pain-sensitive were found in the longitudinal ligaments, periosteum of the vertebrae, loose connective tissue at the surfaces of the annulus fibrosus, ligamentum flavum, lumbodorsal fascia and vertebral diarthroses.[2987]

General therapy of low back pain with little or no regard for a specific diagnosis was discussed. Episodes of acute severe back pain were treated by rest, heat, massage and spinal supports to limit mobility; exercises were not prescribed.[453, 619, 821, 2068, 2269, 2325, 2596] Meprobamate as an adjunct to conventional therapy was thought to be effective.[598] Zoxazolamine was also recommended for treatment of skeletal muscle spasm in older individuals.[2747] [Neither meprobamate nor zoxazolamine has been of much help in our experience.—Ed.] Procaine hydrochloride injected into tender areas or trigger points, usually located over interspinous ligaments or about the sacro-iliac joints, often relieved pain.[453]

Manipulation was recommended during the acute stage of "lumbago" or low back pain from any cause,[619, 2352] though contraindicated by very severe pain, bilateral sciatica, referred coccygodynia, paresthesia in the saddle area, perineum, genitalia or rectum, interference with bladder function related to pain, or impotence.[2352] Manipulation for chronic low back pain had advocates, as usual.[383, 619, 2352] [Manipulation of patients with acute and chronic back pain with no more accurate diagnosis of the causative anatomic lesion than "lumbago" would appear to be an unwise and dangerous procedure.—Ed.] Weight control, posture training, and instruction in protection of the back were also needed.[1893] Patients with chronic low back pain were given exercises as soon as they could be tolerated. These consisted of (1) sit-ups, with knees and hips flexed and hands behind the head, and (2) back extension exercises. By means of a special harness and table, weight was progressively added for resistance.[821] Intermittent traction,

with application of maximal stretch alternating with periods of complete relaxation, was used.[249] Weight reduction in the obese was important.[1387]

Backache from Lumbosacral and Sacro-iliac Sprains and Strains, and from Sacro-iliac Subluxations. Some authors did not consider intervertebral disc disease to be the most common cause of low back pain.[1288, 1289, 1290, 1612, 2287] Others classified most low back pain, other than that caused by disc pathology, under such headings as "acute back strain," "low back strain," "acute lumbosacral" or "lumbar muscle strain."[558,1242] Posterior sacro-iliac ligament relaxation was said to be the most frequent cause of low back disability, and injection of a "proliferating solution" into the relaxed ligament at its junction with bone was recommended.[1288, 1289, 1290] [No other enthusiasts for this therapy have come forward. No control studies were reported.—Ed.]

In an extensive study of low back pain covering 25 years and involving 3,587 patients (64% males), the diagnosis of lumbosacral strain was made in 1,603 patients, "arthritis" in 542, and postural strain in 478. A protruded disc was found in only 83 patients. Diagnosis of sacro-iliac strain was made in 271 patients. Patients with lumbosacral strain associated with congenital anomalies numbered 1,108, and those without anomalies, 495. Results of therapy were better in patients hospitalized for treatment from the onset.[783]

Many disc protrusions resulted from sprains of the lumbosacral joint.[3240] Pain in the low back, which came on suddenly and was related to unusual effort, such as exceptionally heavy lifting or an awkward position in lifting, was attributed to a "strain." Such lesions were the site of hemorrhage and edema; pain was often much more pronounced or incapacitating eight to 12 hours later.[1242]

Differentiation of pain of sacro-iliac joint origin from pain due to a disc lesion depended upon complete relief following injection of 2 c.c. of any suitable local anesthetic solution into each sacro-iliac joint, indicating primary sacro-iliac pathology.[2287] [It is not so simple as this. Relief of pain of myocardial infarction has been reported following chest wall infiltration with an anesthetic agent.—Ed.] "Ligamentous relaxation" resulting from tearing of fibers of the ligaments was said to result in local pain, referred pain, and sciatica. "Prolotherapy" was said to be effective in these cases with "ligamentous relaxation." This consisted of injection of a nontoxic solution of sodium salt of a fatty acid of a vegetable oil combined with Pontocaine, and caused cellular proliferation with increased formation of scar tissue and stabilization of the injected joint.[1288, 1289, 1290] The disability of over 80% of 543 patients treated over a 16-year period,[1288] and of 1,178 patients in another, was permanently eliminated. Improvement occurred within a month.[1289] [The high percentage of patients (94% of 146 consecutive patients) with low back pain considered to have this condition is an unusual experience, which has not been confirmed. No x-ray evidence of increased mobility of structures was cited. No controls were reported. We are skeptical.—Ed.]

Low back pain had a tendency to subside; conservative therapy was in general approved. Bed-rest during the acute stage, application of heat several times daily, and analgesics such as codeine and acetylsalicylic acid every four hours, were recommended, and pelvic traction was of value.[783] With subsidence of acute pain, exercises to strengthen the abdominal and back muscles were initiated and increased as tolerated. Proper posture, with avoidance of hyperextension of the lumbar spine, was of value in preventing recurrences. Weight reduction

in the overweight patient was helpful.[1242] Strapping, braces or other supports were necessary for some.[783]

Industrial Backache. In both the United States and England the most common single reason given for occupational disability (usually attributed to injury) was pain in the back. Acceptance by the physician of a totally inadequate history, with no attempt to determine the extent of actual trauma, was an important factor in the development of a wrongful claim.[1728] An accurate history of the actual mechanics of injury was considered to be very important in arriving at the proper diagnosis.

Examination of 6,523 prospective employees showed congenital anomalies of the lumbosacral region in 41%, and other abnormalities in 19%. The three most frequent congenital defects were malformed lumbosacral articulating facets, spina bifida occulta, and supernumerary lumbar vertebrae. Review of 3,587 employees who sought treatment for low back pain revealed that the largest single group, 31%, also had congenital anomalies.[784] Study of 207 unselected males, most of whom were 18 through 25 years of age, revealed abnormalities in 146 individuals (70% of the number examined). Congenital anomalies accounted for at least 80% of the abnormalities found.[1258] Other studies seemed to indicate that congenital anomalies, per se, were not causes of backache. A three-year survey of industrial back injuries revealed that preplacement back x-rays were of no value in reducing the incidence of back injuries, and that over half of all back injuries occurred within the first 24 months of assignment to a specific job. Radiographically detectable congenital anomalies did not unduly predispose a worker to low back strain.[3303] A comparative study of 200 persons with and 200 persons without symptoms referable to the back showed that congenital defects and structural changes were about equal in number in the two groups. Their presence was considered not clinically significant and not a cause of backache.[1081]

Postural Backache. Poor posture developed during childhood and adolescence, and was prone to cause backache in older individuals, more commonly in women. The characteristic sequence of symptoms consisted of midline aching pain which followed weight-bearing or activity, and was temporarily relieved by sitting or lying with the low back slightly flexed. This pain frequently recurred after a few hours of bed-rest.[558, 1242, 2521] Flexibility of individual segments of the spine was needed to withstand stress and maintain balance.[1827]

Onset of back pain in adult life was attributed to the results of decreased muscle tone. Relaxation of the anterior abdominal muscles resulted in a greater anterior rotation of the pelvis, with increased lumbar lordosis, and strain on the lumbar apophysial joints.[1135] Poor posture, with hyperextension of the low back, also resulted in posterior bulging of the intervertebral disc in this region. Tilting of the pelvis, with increase in the lumbosacral angle, produced a forward thrust, with pressure on soft tissues and articular facets, as well as strain on supporting muscles.[977] A frequent physiologic cause of postural backache was pregnancy. The use of high heeled shoes during pregnancy exaggerated the effect.[1242, 2521] A special syndrome of "hereditary pelvic arthropathy" was found in a mother and daughter.[1027] Conservative measures, which included bed-rest during the acute stage, postural training, and exercises, were recommended.[520, 674, 748, 977, 1242, 1483, 1827]

Spondylolisthesis. Spondylolisthesis caused instability of the low back, led to disc degeneration, and frequently caused low back pain believed to be due to

nerve root compression by disc material, mobile elements of the loose neural arch, or cartilage at the site of the isthmus defect. Oblique roentgen views of the lumbosacral region were sometimes needed to visualize isthmus defects.[1184, 1242, 1827, 3334] Others attributed the pain mainly to muscle spasm.[1274] Spondylolysis or prespondylolisthesis was a pedicle defect without vertebral malalignment, and most individuals with this defect had no backache,[878] but a roentgenographic study of 200 soldiers complaining of backache and 100 normals showed neural arch defects (spondylolysis) to be twice as frequent in the symptomatic group.[993] Degeneration of the intervertebral disc, with instability, apophysial joint changes, and forward displacement of a vertebra in the absence of isthmus defect, was termed "pseudospondylolisthesis."[1274] In a preëmployment x-ray study, 14 of 207 men (7%) had spondylolysis, and nine of these (4.5%) had spondylolisthesis. Frequency was equal in both sexes.[1258]

Though the etiology of spondylolisthesis was not established, several theories were advanced: (1) theory of separate ossification centers, (2) birth fracture theory, (3) theory of fracture during postnatal life, (4) stress fracture theory, and (5) weakness of supporting structure theory. The lesions have not been found at birth.[3335] It was also proposed that the pedicle clefts characteristic of spondylolisthesis were congenital in origin, though often not actually present at birth, and that the break in the pars interarticularis was acquired during childhood, with forward displacement at a later time.[3302] [No evidence to support this theory was given.—Ed.]

In consanguinity studies on families of 24 patients with defective pars interarticularis, incidence was found to be 31.3%, as compared to 5% in the general population. This condition was most likely dominant, and not sex-linked, and had varying expressivity.[3335] [This very interesting study adds weight to the evidence against birth trauma as a cause of this condition.—Ed.]

Conservative measures such as exercises, and support by means of a brace or cast, were first tried.[1242, 1827, 2121, 3334] Stabilization of the back by spinal fusion, in addition to decompression, was often preferred by most authors.[1184, 1242, 1317, 1827, 2121, 2769, 3334] Removal of the posterior arch without fusion was also recommended.[3334] Pseudoarthrosis following attempts at fusion was also reported.[1317]

Reverse Spondylolisthesis. Reverse spondylolisthesis or posterior displacement of a vertebral body over the one below it was not associated with pedicle defects, but was a consequence of intervertebral disc degeneration, with instability of the involved apophysial joints. This was seen most frequently as a posterior displacement of the fourth lumbar on the fifth lumbar vertebra. In the absence of any roentgen abnormalities other than vertebral body displacement or anteroposterior sliding, this has been termed "primary" instability of the lumbar vertebrae. When the interspace was narrowed, or there were evidences of arthritis or spondylolisthesis, such displacement was termed "secondary" lumbar vertebral instability.[871, 2198] [Posterior spondylolisthesis is not at all rare, is found frequently among patients with severe spinal osteoarthritis, and generally causes no special difficulties.—Ed.]

Osteoporosis. Relatively few papers dealt with osteoporosis as a cause of backache. Some individuals, even some with severe degrees of osteoporosis, were asymptomatic. However, pain was commonly associated with this condition.[1511, 1544, 1734, 2058, 2486, 2487, 3278] Onset of pain varied from the gradual development of

vague, indefinite aching, to severe, constant back pain. This severe pain was often well localized, and was sometimes sudden in onset, as when it was associated with an injury, often of a minor nature, to the back. Compression fracture of a vertebral body, with spinal nerve root compression, was believed to be the cause of the severe pain which often radiated from the back into the buttocks or around the trunk, but a sciatic distribution was rather unusual. Movements of the back or jarring of the spine aggravated the pain. A decrease in height, increase in dorsal kyphosis, muscle spasm, tenderness over the spinous processes, renal colic, and limitation of flexion of the spine were the symptoms and physical findings sometimes observed. [The cause of pain associated with spinal osteoporosis in the absence of compression remains obscure.—Ed.]

Roentgen findings of decreased density of the bones of the spine and pelvis were necessary to the diagnosis, but decreased bone density alone did not establish the diagnosis. Osteomalacia, myeloma, metastatic malignancy, hyperparathyroidism, Cushing's syndrome and hyperthyroidism sometimes produced the same roentgen findings.[2724] [Iatrogenic steroidal excess is one of the more common causes today. One of us (E. F. R.) does not agree, but attributes the osteoporosis to R.A., and the spinal fractures to the increased activity which accompanies pain relief. —Ed.] The bone density approached soft tissue density, so contrast was diminished. Intervertebral discs tended to expand, and compressed the end plates of the adjacent vertebral bodies, with production of the biconcave appearance, termed the "fish-tail" or "cod-fish" vertebrae.[734, 1511, 1544, 2058, 2486, 2507] It was estimated that from 30% to as much as 60% of the calcium content of bone had to be lost before decreased density could be definitely detected radiographically.[3278]

Osteoporosis was a serious hazard of corticosteroid therapy, especially in postmenopausal women. Some of the diseases for which steroids were used, such as R.A., were themselves associated with osteoporosis of varying degrees.[2060] [Iatrogenic osteoporosis is discussed in more detail in the Section on Steroid Therapy of R.A.—Ed.]

Osseous changes and fractures occurring with the malabsorption syndrome (osteomalacia due to sprue) were described.[1359] A patient with xanthomatous biliary cirrhosis had an associated severe "osteoporosis."[1176] [Differentiation between osteomalacia and osteoporosis was impossible on the basis of the data and therapy.—Ed.] Osteoporosis could be due to or associated with adult rickets, multiple myloma, hyperparathyroidism, metastatic carcinoma, long-standing renal insufficiency, thyrotoxicosis, and Cushing's syndrome.[1511, 2153]

In a series of 42 osteoporotic patients, all women between the ages of 53 and 87 years, with fractures of the spinal vertebrae, fractures were all of the compression type, and most followed slight trauma. It was considered to be injurious or even dangerous to immobilize these patients. The earliest possible restoration of mobility was considered to be the best treatment.[1734]

Therapy was directed toward the basic cause of osteoporosis in those patients having hyperthyroidism or Cushing's syndrome.[3260] In others, an adequate diet which fulfilled the needs for protein, calcium and calories, plus a supplement of calcium or strontium, the use of androgens and estrogens in effective amounts, and as much activity as was consistent with the patient's capacity, were recommended.[2686, 2794, 3260] [There is no evidence that recalcification of the bones occurs with this therapy. Symptomatic improvement occurs with time alone.—Ed.]

The effect of strontium was discussed,[2686] but its value in the treatment of

osteoporosis has not been definitely established.[2175] [Further study of its use is desirable.—Ed.]

There was little evidence that hormone therapy increased bone density,[2058, 2174, 3278] but a combination of androgen and estrogen provided the most potent and practical anabolic preparation for the control of senile osteoporosis.[2510, 2512, 2724] [Symptoms at times are relieved. The degree of calcification is not changed.—Ed.] A mixture of 90 mg. testosterone enanthate and 4 mg. of estradiol valerate per milliliter, given intramuscularly in a 1 to 2 ml. dose every three or four weeks, appeared to have an optimal adrogen-to-estrogen ratio and to be effective in relieving pain. [With time alone, compression fractures become painless.—Ed.] Estrogens, such as estradiol benzoate and diethylstilbestrol, and androgens, such as testosterone propionate, given separately, have been in use for some time.[2153, 2175, 2486, 2686, 3260] The most serious complication of androgen treatment was masculinization in the female,[690] but few patients of either sex have had undesirable side-effects.[2512]

Osteoporosis due to cortisone was a relative indication for withholding additional steroid therapy. Use of anabolic therapy was advocated as corrective therapy. Use of the combination of estrogen and androgen as a preventive measure was encouraged for all patients on prolonged steroid therapy, especially postmenopausal women, or individuals with hypogonadism and normal adrenocortical function.[2506, 2508, 3260] [Two of us (E. F. R. and F. E. D.) are emphatically opposed to this view. Some of us use this combination if there is any evidence of diffuse skeletal rarefaction. None uses it routinely—Ed.]

A vibrating bed reduced calcium loss in normal individuals and, by analogy, should be useful in providing stresses and strains to bones of immobilized osteoporotic patients.[2175] Analgesics, and the use of a corset or torso jacket or a light weight brace, could be of benefit.[2153]

Hypertrophy of the Ligamentum Flavum. This uncommon cause of low back pain and sciatica was mentioned only occasionally.[2415] Hypertrophy was really a misnomer, as the thickening was due to fibrosis secondary to damage of the elastic tissue. Myelograms were usually normal, but might show a posterior extradural defect. This condition was to be considered when a convincingly disabled patient had few objective signs.[2415, 3073]

Malignant Disease of the Spine. Carcinoma was not a common cause of back pain, and usually back pain was a late symptom of a malignancy. [Nevertheless, it should always be considered in cases of severe, persistent back pain of unexplained origin.—Ed.] Extensive bone metastases caused increasingly severe back pain, present all the time and requiring narcotics for relief.[77]

Absence of back pain and of reflex changes directed attention to the femur as the site of the lesion.[1184] Carcinoma of the breast, kidney, thyroid, prostate, lung and stomach metastasized to bone.[36, 77, 558]

Myeloma, solitary or multiple, presented with localized, intermittent back pain, which later became persistent and more severe. Bence Jones protein was found in the urine in about half of the cases.[77, 558, 1827] [Of greater diagnostic value than the comparatively crude chemical test for Bence Jones "protein" is the presence of an abnormal "myeloma protein" band in the electrophoretic strip of urine of many patients with myeloma.—Ed.] The pain of osteosarcoma often resembled that of arthritis of the spine or a back sprain, and was sometimes mild at the

onset. Back pain also occurred with chordoma, retroperitoneal metastases from testicular tumors, or perineural sheath invasion by prostatic carcinoma.[77]

Gynecologic Lesions. As a single symptom, backache was seldom the result of pelvic disease. It was seen with dysmenorrhea and dyspareunia in endometriosis or pelvic inflammatory disease. A fixed, tender, retroverted uterus with adnexal masses sometimes caused a backache which was relieved by surgery, but this was unusual.[2082] "Nearly all backaches of childbearing were postural in origin." Pain in the pelvis due to relaxation of the ligaments, with some mobility of the pubic symphysis and sacro-iliac joints, was said to be excessive and allowed considerable painful movement. This pain was localized to the lower abdomen on walking, and often first appearing during the puerperium. Roentgenograms showed widening of the joint space at the symphysis. Rest and support were necessary for a few weeks.[2521] Large fibroids, endometriosis, and intrapelvic malignancy sometimes caused backache and pain with sciatic distribution.[2960]

Gastrointestinal Tract. Back pain appeared at times with a number of abdominal conditions. It was frequently very severe and poorly localized, and often was neither initiated, aggravated, nor relieved by movement of the back or by rest of the back.[558] Pain in the dorsal spine, midline or lateral in location, was found to be caused by peptic ulcer in a number of patients. [Back pain is rarely seen without other classic features of peptic ulcer.—Ed.] Of 68 patients with dorsal pain and spinous process tenderness, 23 had demonstrable ulcers, 15 had scarring and distortion of the duodenum from previous ulceration, and six had duodenitis. Tenderness over the sixth and seventh dorsal spinous processes was also observed in several patients with silent ulcers.[1604] Low back pain was reported to be associated with anorectal disease, usually anal fissures or prolapsed hemorrhoids, singly or combined.[2046]

Lumbodorsal Syndrome. Fibrosis of subfascial fatty tissue was said to develop with regularity at two sites, one in the lumbar region and the other in the sacral region. The midlumbar syndrome (second lumbar nerve) was characterized by pain in the low back, with radiation into the region of the hip, and less commonly to the groin and inner aspect of the thigh. Tenderness was located over or near the sacro-iliac joint, or over the outer portion of the sacrospinalis muscle. The midsacral syndrome (first sacral nerve) was characterized by pain in the low back, buttocks and the lateral aspect of the thigh and leg. Tenderness was usually found in the gluteal muscles. The trigger point was searched for in the paraspinal region at the level of the third sacral segment. Infiltration of the subfascial tissue at the trigger point with a local anesthetic (2% procaine hydrochloride) and surgical resection of the deranged structures were said to relieve pain. The cause of this lesion was considered to be a rupture or tear of the lumbodorsal fascia, with fibrosis of the subfascial tissue and adhesions between these structures.[781, 782] [It is difficult to evaluate these papers. —Ed.]

Spinal Osteochondritis (Adolescent Kyphosis); Juvenile Epiphysitis; Scheuermann's Disease. This condition was again noted to affect young individuals between the ages of 12 and 17 years, and to be more frequent in boys than in girls. A mild kyphosis or increased curve involved most frequently the mid and lower dorsal spine. Pain, when present, was usually not severe.[558] In the early stages, roentgenograms showed the fragmented epiphyses and anterior

wedging of the vertebral bodies.[1749] A Schmorl's node or herniation of the nucleus of an intervertebral disc into an adjacent vertebra, the so-called intracancellous disc prolapse associated with the irregular vertebral end-plates, was considered to be an advanced roentgenographic finding of osteochondritis.[850, 1258] [Vertebral intrusions indistinguishable from Schmorl's nodes are common with several disorders of the spine other than Scheuermann's disease.—Ed.]

Osteochondritis of the lumbar spine, called osteochondrosis juvenilis lumbalis, usually occurred in otherwise healthy teen-age boys.[2238] A study of 30 patients with osteochondritis juvenilis lumbalis from a much larger number of patients with the usual type of Scheuermann's disease was reported.[851] Treatment consisted of limitation of activity, with special care not to carry out any forced flexion exercises. A few weeks of bed-rest or a plaster jacket was only sometimes needed. The prognosis was excellent.[2238]

Backache from Diseased Articular Facets. A causal relationship between low back pain and lesions of the spinal joints or articular facets was not readily established. Degenerative changes of the zygapophysial joints, frequently shown by x-ray, could not be related to a given clinical picture.[67, 1242]

Backache from Congenital Anomalies. Congenital variations in structure of vertebrae, especially in the lumbosacral area, were common. During the first three or four decades of life these anomalies did not show a good correlation with low back pain. Defects observed on examination of spine films, such as spina bifida, asymmetry of facets, lumbarization of the first sacral segment, sacralization of the fifth lumbar vertebra, and spondylolysis, did not in themselves cause backache and pain, but predisposed, through inaccurate articulation, to early symptomatic degenerative joint disease, or, in combination with poor posture, to chronic low back strain.[558, 1242] In a study of the lumbosacral region of 207 unselected men, most between the ages of 18 and 25 years, over 80% of the abnormalities were found to be congenital anomalies. Spondylolisthesis, spondylolysis, posterior displacement of the fifth vertebra on the sacrum, sacralization of one or both sides of the fifth lumbar vertebra, and lumbarization of the first sacral segment, were considered to be disqualifying for heavy work.[1258] In a study of roentgenographic abnormalities of soldiers, the incidence of congenital variations, such as spina bifida occulta and transitional lumbosacral vertebrae, was found to be practically the same in a group with backache and in a control series. However, the number of neural arch defects (spondylolysis) in the spines of those complaining of backache was found to be two and a half times that of the control group.[993] Anomalies of the fourth and fifth lumbar and the first sacral segments were important, especially in younger individuals.[1406] Spondylolysis sometimes occurred unilaterally in the lumbar spine, and caused no symptoms until trauma was sustained.[1893] Movements between these joints caused friction and irritation, and resulted in backache.[624]

A number of anomalies found on roentgenograms could be interpreted as fractures. Many of these were due to ununited secondary ossification centers for various spinal processes. These were said to be more frequent in men, and usually involved the second or third lumbar articular processes.[1293] [The reproductions of roentgenograms and illustrations of the lesions are outstanding.—Ed.] Of 100 cases of spina bifida,[496] 23 patients had myelocele or meningocele and 77 had spina bifida occulta. Lower lumbar and sacral segments of the cord were most frequently affected.

Psychogenic Backache. Several authors considered the functional overlay, so frequently associated with backache from any cause, as the common incapacitating component. Backache due entirely to an emotional or a psychiatric cause was considered to be a rarity.[120, 1904, 3013, 3089] It was suggested that many alleged psychosomatic backaches had some undiscovered physical cause.

Factors involved in production of disabling backaches from relatively minor organic lesions included: (1) anxiety, with magnification of the severity of backache; (2) emotional factors and their effects on muscular tension; (3) oversensitivity to pain; (4) lack of distractions; (5) suggestibility; and (6) gainful results from back pain.[120] A positive diagnosis depended upon the demonstration of the way in which backache fulfills an adaptive role in the emotional life of the patient.[1904]

Malingering was often difficult to differentiate from psychogenic backache. Inconsistency of physical findings, widespread tenderness, and the absence of objective evidence of disease proportionate to subjective complaints suggested malingering.[1827] The saline-procaine test was used to differentiate local trigger-point disease from malingering, hysteria, and underlying disc or joint disease. When injection of the tender site with procaine relieved radiation of pain, and when the pain did not recur in the identical spot, a local process or trigger-point disease was inferred. If pain and radiation did recur, underlying disc or joint disease was suspected. A variant of this test, using normal saline solution, was employed. Conversion or malingering was suspected when neither normal saline solution nor procaine hydrochloride solution led to a decrease in pain.[1440] [There were no data that indicated the efficacy of these procedures.—Ed.]

Osteitis Condensans Ilii. This fairly uniform triangular area of increased density in the lower portion of the iliac bone lay adjacent to but did not involve the sacro-iliac joint. It was unilateral or bilateral. A total of 67 cases, all adult females (80% had been pregnant), was collected in a "few years" from roentgenographic findings of patients having x-rays, usually for conditions other than back pain. Some were followed for as long as six years. The pubis showed irregular sclerosis in a few cases. In no instance did the sclerotic area diminish in size or density.[3279] [A recent report, with illustrative x-rays, showed that these radiologic lesions do decrease in size, or even disappear in some cases (Jacqueline, F., and Arlet, J.: Arthritis and Rheumat. **2**: 8 [Feb.] 1959).—Ed.] Onset following pregnancy, lack of stiffness, normal or nearly normal spinal movements, lack of systemic symptoms, normal erythrocyte sedimentation rate and intact sacro-iliac joint margins were characteristic of the condition.[1247, 3085]

Other Causes of Backache. Herniation of fat lobules through fascia in the lower back region was again cited as a cause of backache or sciatic pain, or both.[2760] [The excessive initial popularity of this presumed cause of backache has not been sustained. —Ed.] Four more cases of meningeal diverticula of sacral nerve roots, so-called perineural cysts, demonstrated by x-ray and causing low backache, were proved at operation. Isolated globular collections of contrast material in the sacrum some time after myelography established the diagnosis of diverticula of nerve roots. No motor, sensory, or reflex changes were found. The nerve fibers were stretched but not destroyed, and pain was the only neurologic symptom.[3010] Aneurysmal bone cysts, consisting of irregular blood-filled spaces, occurred in the spines of children and young adults.[210] The etiology was unknown. Six of the seven patients in this series had originally been considered to have giant cell tumors of the spine. Back pain was the main symptom. Encroachment on the spinal cord occurred in three patients.[210]

Back pain was also associated with brucellosis of the spine,[3177] chordoma,[2018] dissecting aneurysm, spinal subarachnoid hemorrhage, and renal vein thrombosis.[637]

Backache and Sciatica from Diseased Intervertebral Discs

Although reports concerning intervertebral disc disease have diminished in the last 10 years, the general problem was quite widely discussed.[61, 139, 527, 871, 1440, 2227, 3244] Intervertebral disc disease was again considered by some authors to be a common cause of backache.[363, 1612, 2599, 3312] Of 3,587 cases of back pain studied over a 25-year period, protrusion of the intervertebral disc was considered to be the cause in only 83 patients, an incidence of 2.3%.[783] In another series of 2,000 patients with back pain, 445, or 22.3%, were suspected of having intervertebral disc protrusion; sciatic pain occurred in 324, or 76% of these.[1126] Osteoarthritis associated with primary instability of the lumbar vertebrae (pseudospondylolisthesis), or reverse spondylolisthesis, was thought to be due to intervertebral disc degeneration.[871] Disc degeneration with osteoarthrosis of the spine was more common in the male, though osteoarthritis was more common in the female.[1668]

Anatomy and Physiology. Several authors reviewed the anatomy of the intervertebral discs.[454, 731, 2360, 2599, 2600, 2681] Poor blood supply predisposed to degenerative changes and to poor repair following injury. The nucleus pulposus consisted of a soft, gelatinous material, the remains of the embryonic notochord. With advancing age, this structure was invaded from the peripheral annulus by fibroblasts, cartilage cells, and collagenous fibers. The original notochordal cells decreased in number, and the nucleus became denser and drier, and yellowish in color. Nutrients diffused through the porous cartilaginous end plates from the vertebral bodies. The disc between the fifth lumbar vertebra and the sacrum formed the largest mass of avascular tissue in the body. The peripheral fibrocartilaginous annulus fibrosus was made up of laminae which encompassed about half of the nucleus fibrosus. The ends of the laminae became attenuated or bifurcated to enclose the ends of adjacent laminae. The lumbar curve widened the intervertebral disc anteriorly and compressed it posteriorly. The annulus of the disc then bulged back into the vertebral canal. It was suggested that the structure of the disc was better fitted to withstand tension than pressure, and that local conditions in the lumbar spine led to degenerative changes.

Other structures of importance were the anterior and posterior spinal ligaments, the ligamentum flavum and the dentate ligament. The ligamentum flavum was attached to the anterior surface of the laminae above and to the posterior surface and upper margins of the laminae below. The dentate ligaments which anchored the spinal cord lay between the anterior and posterior nerve roots, and were attached to the lateral aspects of the cord on one margin and to the inner surface of the dura laterally on the other.[731, 2599] The disc had pain fibers in the annulus, and compression could be painful, as was demonstrated by injection of saline solution directly into the disc.[1827] Tumors of nerve trunks or roots of the spinal cord were frequently painless; pressure or tension in tissues was not the primary stimulus for pain, although it was a secondary factor in tissues already hyperalgesic. Since lumbar intervertebral disc protrusion sometimes compressed nerve roots without causing pain, it was suggested that pressure on nerve roots was not a common primary cause of sciatic pain.[1680] [Most authorities would not agree with this concept.—Ed.]

It was suggested that the hydrophilic properties of the nucleus pulposus had some bearing on the development and symptomatology of the disc syndrome, through increasing pressure within the nucleus pulposus. Pressure differences were influenced by the hydrophilic mucopolysaccharide content, the concentration of protein gel, and the

presence or absence of cavities in the nuclei, as well as the variations in elasticity of the annulus fibrosus.[454] The tendency to crystallization, and precipitation of collagen after the age of 30, inhibited uniform transmission of stress to the annulus, so that weakening and rupture of fibers might eventually lead to herniation of the nucleus.[2244] Chromatographic investigations of extracts of minced nucleus pulposus indicated the presence of chondroitin sulfate, hyaluronic acid, and keratosulfate types of mucopolysaccharide.[1305]

Pathology and Pathogenesis. The pathology of disc degeneration was discussed.[1180, 1181, 1749, 1827, 1899, 2599, 2600, 2681, 3244] It was difficult to draw the line between physiologic degenerative changes and definite pathologic changes. With protrusion of the nucleus pulposus, the disc flattened and lumbar instability developed. This led eventually to loss of alignment of the apophysial joints, characterized in some instances by overriding of the facets, pseudospondylolisthesis, and reverse spondylolisthesis.[871] Narrowing of the discs was common in the aged. A study of 117 cervical spines of white males between the ages of 74 and 96 years showed flattening of the bodies of the cervical vertebrae, espcially from the third to seventh cervical. Hypertrophic arthritic changes increased with age.[1034] Covertebral osteophytes, secondary to cervical disc degeneration, sometimes impinged on the vertebral artery and its surrounding sympathetic plexus, or, more posteriorly, upon the intervertebral foramen.[1294]

Study of thoracic discs showed that radial ruptures from the disc centers were found as commonly in the thoracic spine as in the cervical and lumbar spines. These radial ruptures tended to occur on the concave side of spinal curvatures in all regions.[1899]

Relationship to Trauma. Disc protrusion occurred when a person bending forward with the spine flexed either lifted, or was struck on the upper back or shoulders, or when he straightened up to a standing position with a twisting motion.[3244] In a series of proved protrusions, onset in a surprisingly high number dated to a spinal anesthetic.[2681] [It would be of interest to know how the levels of the protruded discs in these cases corresponded to the level at which the spinal needle was inserted.—Ed.]

"Whiplash" injuries have assumed an importance indicated by the number of papers on this subject.[44, 170, 247, 261, 1374, 1827, 2040, 2070, 2204, 2442, 2728, 3370] These injuries to the neck were caused by "jerking" of the head and neck in automobile accidents, particularly rear-end and side collisions. They were therefore further complicated by medicolegal implications. Cervical disc injuries and typical disc syndromes were rarely associated with this type of accident;[44, 261, 1374, 2040, 2070, 2204, 3370] cervical disc protrusions were sometimes not even mentioned.[170, 247, 1780, 2728] A study of 40 consecutive cases failed to reveal a single proved disc injury,[2204] as did another study of 66 patients.[2070] [Though many not particularly interested in traumatic surgery have assumed cervical disc injury was a frequent finding in these cases, it appears to be extremely unusual. However, the late findings of spondylosis may be shown to be more frequent. "Whiplash" injuries are also considered in the Section on Brachialgia.—Ed.]

Calcification of Intervertebral Discs. Idiopathic disc calcifications were classified by one group as (1) disappearing, (2) dormant, and (3) silent. The "disappearing" form was symptomatic; eventually, calcifications disappeared. The "dormant" form developed acute symptoms after the calcified disc had been found by chance. In the "silent" form, the asymptomatic calcification was an incidental finding.[2484] Calcification of intervertebral discs was observed during childhood. Cervical and dorsal discs were frequently affected, and reported in-

cidence was slightly higher in males. Pain, limitation of motion, muscle spasm, and occasionally mild deformity were found in a majority of patients. This condition sometimes appeared to follow injury to the head and neck, more often an acute inflammatory process.[2272] In some children, calcified discs were multiple and affected the nucleus pulposus. The calcification was reversible, and usually disappeared after a variable period of time. Eighteen new cases were reported (17 children and one adult).[270, 1087, 2272, 2371, 2484, 2542, 3214] In two the calcification had penetrated the annulus fibrosus and had protruded.[270] A third patient had a herniated calcified thoracic disc with spinal cord compression. Surgical removal resulted in complete recovery.[2371] Three other patients also had calcified material in the paravertebral tissues.[2272] Calcified discs in elderly individuals were believed to represent a degenerative process.[2272] Calcification of discs in the adult suggested ochronosis, and the finding of alkaptonuria would confirm the diagnosis. [This is reviewed in the section on Alkaptonuria, Ochronosis, and Ochronic Arthritis.—Ed.]

Cervical Discs. Several authors discussed the well known syndrome of protrusion of the nucleus pulposus of cervical vertebrae.[429, 928, 2300, 2599, 3387] Asymptomatic disc protrusions were mentioned.[2093] [There is some question about the relationship of disc protrusion syndromes, foraminal syndromes due to osteophytes, and the syndromes of cervical spondylosis and other cervical conditions, such as thoracic outlet syndrome, hyperabduction syndrome, and scalenus anticus syndrome. Differences in terminology and classification account for most of the apparent discrepancies.—Ed.]

A study of 246 patients with surgically verified disc herniations over a 16-year period was reported. These patients were divided into four groups, according to the type of intervertebral disc protrusion: (1) unilateral soft disc protrusion with nerve root compression (175 patients), (2) foraminal spur, or hard disc, with nerve root compression (46 patients), (3) medial soft disc protrusion with spinal cord compression (14 patients), and (4) transverse ridge or cervical spondylosis with spinal cord compression (11 patients). [This grouping seems reasonable, and will be used for the purpose of the discussion to follow.—Ed.]

(1) *Unilateral soft disc protrusion:* The unilateral soft disc protrusion frequently followed trauma, came on suddenly, and was characterized by aching and stiffness of the neck and by pain in the lower portion of the posterior neck or upper dorsal spine and region of the scapula. Pain varied from a mild ache or pain starting insidiously, to excruciating, sharp, stabbing pain which came on suddenly and was aggravated by movements of the head and neck, especially rotation, lateral flexion toward the side of the lesion, or forward flexion. Radiation of pain from the neck into the shoulder, arm, forearm, wrist, hand or fingers occurred, usually soon after the onset of pain in the neck. The site of the pain and paresthesias in the upper extremity depended upon the level of the disc affected.[161, 368, 370, 429, 928, 2599] Pain was usually aggravated by factors which elevated the intraspinal pressure, such as coughing, sneezing or straining, by mechanical alterations of the spine such as rotation or flexion, and by stretching the nerve roots, as in letting the arm hang idly at the side. Relief was sometimes obtained by elevating the extremity or by placing the hand behind the neck, thus partially relieving traction on the nerve root.[2599]

Symptoms and signs in 100 patients with confirmed protrusions of single cervical discs showed that nerve root C-5 was involved in two, C-6 in 19, C-7

in 69 and C-8 in 10 patients. Sensory symptoms or objective changes in the digits and localized muscle weakness were most reliable in localization of the lesion to one root. An accurate history and careful neurologic examination made exact nerve root diagnosis possible in 87 of the 100 patients.[3387] [Spastic quadriparesis with C-4 disc has been observed by one of us (G. M. W.)—Ed.]

(2) *Foraminal narrowing by osteophytes with spinal nerve root compression:* Foraminal narrowing by osteophytes or hard discs, with spinal nerve root compression, often due to or associated with degenerative changes in the disc, caused the same clinical symptoms and findings as did lateral nucleus pulposus protrusion. Further disc thinning and increased pressure caused the development of osteophytes, which sometimes extended posterolaterally into the foramen, or forward toward the vertebral artery in the transverse foramen. These changes caused straightening of the cervical curve and telescoping of the posterior apophysial joints. Overriding of these articular surfaces often stimulated spur formation about the margins, with further narrowing of the foramen.[255, 1294, 1724, 3369] The distribution of pain, paresthesias, muscle spasm, motor weakness, and reflex changes, as in the soft disc protrusion, depended upon the root or roots affected.[1294, 1724] Compression of the vertebral artery, and the sympathetic network of nerves accompanying it, by osteophytes extending posteriorly caused a migraine-like syndrome. Other symptoms associated with this condition included ataxia, dizziness, diminished hearing, buzzing in the ears, burning sensation of the posterior portion of the tongue, soreness and pain in the pharynx, burning or prickling sensation in the throat, and difficulty in swallowing. This was termed the *Barre-Lieou syndrome.* Interference with vertebral artery circulation to the lower pons and medulla, where nuclei of the cranial nerves are located, was believed to be a factor in the development of this syndrome.[1831, 2727, 3369]

(3) *Medial soft disc protrusions (acute protrusion of nucleus pulposus):* Medial soft disc protrusion, with spinal cord compression rather than root compression, presented a different picture. A protrusion lying lateral to the center of the spinal canal often compressed the spinal cord on one side and produced a Brown-Séquard syndrome. As a rule, the central protrusion compressing the anterior portion of the cord produced a disturbance of motor involvement of the lower extremities. This included difficulty in walking, due to muscular spasticity, unsteadiness and uncertainty of gait, and muscular weakness starting in the feet and extending upward. Tendon reflexes were exaggerated. Sensory changes were mild and variable. The sensory level was often misleading. Urinary difficulty sometimes developed. This condition was frequently confused with multiple sclerosis, amyotrophic lateral sclerosis, and subacute combined degeneration or arteriosclerotic changes of the spinal cord.[429, 2599] Compression of the spinal cord at a midcervical or higher level sometimes caused greater impairment of the kinesthetic sense of one or both upper extremities than of the lower extremities. Therefore, loss of proper control of one or both upper extremities due to impaired postural sensibility warranted suspicion of a lesion involving the cervical portion of the spinal cord.[722]

(4) *Cervical spondylosis:* Transverse ridge or cervical spondylosis with spinal cord compression was a popular subject.[368, 370, 444, 571, 999, 1831, 2360] The etiology of cervical spondylosis was complex. A generalized degenerative process involving the intervertebral discs was probably the cause in patients with multiple disc

involvement at all levels of the spine. A single disc lesion suggested recent or old localized trauma or occupational trauma. The normal wear and tear of an extremely mobile cervical spine sometimes led to degenerative changes. Frequently a disc adjacent to congenital fusion of two vertebral bodies showed degenerative changes. Disc protrusions were of two types: (a) herniation of the nucleus pulposus following rupture of the annulus fibrosus, and (b) disc degeneration with bulging, increased bone proliferation, and the formation of a posterior osteophyte composed of bone, fibrous tissue and cartilage. Such an osteophyte did not always occur at the site of disc degeneration. Osteophytes often fused and formed a ridge overlying the bulging disc, and thus compressed or indented the anterior aspect of the spinal cord, interfering with circulation of the cord through pressure on the anterior spinal artery.[368, 999, 2360] Cervical myelopathy, a complication of chronic degenerative changes in the cervical spine (cervical spondylosis), needed to be differentiated from the acute intervertebral disc syndrome. Root involvement and sensory phenomena of cord pathology occurred in a high percentage of patients. Motor symptoms, usually weakness, occurred in one or both lower extremities, and much less often in the upper extremities. Pain in one or both upper extremities and in the neck occurred quite frequently.[571] Pain in the neck and upper extremities and in the leg, resembling sciatica, was also reported.[3116] Large anterior osteophytes occasionally distorted the esophagus and caused sensory symptoms and pain on swallowing.[368, 1831] [This must be quite rare.—Ed.]

Of 40 patients with cervical spondylosis, 23 had radicular syndromes, 12 had spinal cord syndromes, and five had neither radicular nor spinal cord involvement. Half gave a history of trauma to the head and neck. The radiologic findings in the cervical spine were not accepted as a cause of the patient's symptoms without critical clinical assessment. Myelography was seldom needed. Conservative treatment was advocated for patients over 50 years of age.[444]

A new diagnostic sign for herniation of a cervical disc involved voluntary compression of the cervical spine, and combined this with Valsalva maneuver, which intensified the effect by increasing the intraspinal pressure. This test combined Naffziger's jugular compression test and Spurling's cervical spine compression test.[968]

Thoracic Discs. Protrusion of a thoracic intervertebral disc was a rarity but occurred with about equal frequency in both sexes. No predisposing factors were determined. One series of 15 adults[5] and another of 10 adults were reported;[1733] also, one child with protrusion of a calcified thoracic disc,[270] and one child with protrusion of a calcified thoracic disc and spinal cord compression.[2371] Single adult cases, one with protruding thoracic disc producing pressure on the spinal cord,[678] and the other presenting a protruded calcified thoracic disc lying under the posterior longitudinal ligament,[1748] were also reported. Multiple calcified discs in children were usual, but protrusion was limited to a single disc.[270]

Diagnosis of a thoracic disc protrusion was difficult, often requiring myelogram, oblique views, and slow movement of the contrast material. Early surgical treatment of those patients presenting evidence of spinal cord compression was essential.[5, 6, 1733] Fenestration of the disc (evacuation of the degenerated disc center through an incision in the annulus fibrosus, outside the vertebral canal) was effective in relieving spinal cord compression in a 36 year old woman.[678]

Lumbar Discs. The general problem of lumbar disc protrusions was reviewed.[50, 363, 364, 743, 744, 1570, 1827, 2227, 2600, 2681, 3244, 3312, 3334] Sciatic pain extending below the knee, flattening of the lumbar curve, sciatic scoliosis or "list," accentuation of pain by flexion, coughing, sneezing or by extension of the spine, and a positive straight leg raising test, all pointed toward the diagnosis of a lumbar disc protrusion. Spinal nerve root compression was suspected when sensory disturbances over affected dermatomes were present, and deep reflexes were diminished or absent. Weakness of the dorsiflexors of the great toe, or inability to "stand on tiptoe" on the affected side, was a valuable sign.[364] Tenderness over the gluteus muscle, a handbreadth below the posterior superior spine of the ilium, over the superior gluteal nerve (derived from the posterior branches of the fourth and fifth lumbar and first sacral nerves), was consistently present in over 90% of proved disc extrusions.[3244] In some patients, tingling and numbness in the distribution of radiating pains were felt intermittently or continuously.[2600] Pain in the groin or lower abdomen, and testicular pain with tenderness extending along the spermatic cord, were most bothersome before root pain became a prominent symptom.[363] Distribution of the abdominal pain, most commonly in association with protrusion of the disc between the fourth and fifth lumbar vertebrae, did not correspond to the relevant dermatome, and was believed to be referred pain, conveyed by the sinuvertebral nerve, composed of sympathetic and somatic fibers.[975]

Massive protrusion of a lumbar disc sometimes compressed the cauda equina, and sometimes caused lower extremity paralysis as the first significant manifestation, though more commonly this occurred as a complication during an ordinary attack. Such a lumbar disc lesion frequently did not respond to conservative treatment, and constituted a threat to the patient's life.[1570] Five patients with partial paraplegia and with bladder and bowel dysfunction were mentioned.[3244] Two other patients with extensive paralysis from protruded lumbar discs were reported.[743] The records of 21 patients with protruded lumbar discs and weakness of the legs were reviewed. This group made up 0.5% of more than 4,000 patients operated on for protruded discs in a five-year period at the Mayo Clinic. In a few, muscular weakness developed suddenly, but in most it was progressive. In three patients there was no return of function after surgery, while in five the operative results were excellent. Early surgical treatment was considered to be essential to recovery.[2998] [These cases should be considered as surgical emergencies. They constitute the one group in which the outcome may be fatal. Manipulation of the back or conservative therapy is contraindicated.—Ed.]

Osteochondritis of the lumbar spine might, in some patients, have resulted from a disease of the discs, and secondary functional disturbance of the ossification centers in the vertebral epiphysial rings.[2238] The ninth published case of surgically treated lumbar disc herniation in children under 16 years of age was that of an 11 year old girl who is now the youngest reported.[976] Two children, aged six and 13, with protruded intervertebral discs and dystrophic features (multiple anomalies), were reported. A disturbance in the "anlage" of the discs was regarded as the chief cause of intervertebral disc protrusion at an early age.[1686]

Diagnosis. The clinical findings necessary for making a diagnosis were reviewed.[50, 61, 139, 363, 364, 444, 744, 1570, 2227, 2599, 2600, 2681, 3244, 3312, 3334] Elements for the diagnosis of intervertebral disc protrusion syndromes have been widely re-

ported in the last several decades. Some believed the diagnosis was made too readily, too often, and on insufficient grounds. The history and physical findings, especially the neurologic findings, were considered by most clinicians to be grounds for a tentative if not definitive diagnosis. Roentgenograms were valuable in excluding certain lesions. Myelograms were sometimes needed to determine the level of disc protrusion. It was urged that the primary diagnosis in these patients be in terms of root compression as "compressive radiculitis" or "compressive cauda equinitis." The causes of compression, such as disc protrusion, tight dural sheath, or tumor, were secondary in importance to the basic process.[2227]

Fractures and dislocations associated with severe trauma seldom posed diagnostic problems. Tuberculosis and other infections of the spine usually caused systemic manifestations, and ronetgenographic findings eventually led to the diagnosis. Spondylolisthesis with instability of the affected segment, recognizable on roentgenograms, frequently presented typical findings, and was often associated with disc degeneration and protrusion of disc material.[364] [This is not an "either-or" condition, as this congenital anomaly may be and usually is asymptomatic until "decompensation" of the musculature and ligamentous structures or disc degeneration and instability of the segment leads to symptoms.—Ed.] An extensive spina bifida, especially when associated with a tuft of hair, dimple, sinus or localized node or lipoma, suggested the possibility of a congenital intraspinal tumor. Rheumatoid (ankylosing) spondylitis, early in its course, often presented a diagnostic problem. Roentgenographic changes in the sacro-iliac joints eventually gave the answer. [See Section on Rheumatoid Spondylitis.—Ed.] Any deep mass along the proximal portion of the sciatic nerve, or a foreign body or abscess in the gluteal muscles, presented a problem. The lesions of herpes zoster appeared within a few days of the onset of pain. Chordomas, osteogenic sarcomas, osteochondromas, cauda equina tumors, and spinal cord tumors were at the onset often suspected of being posterior disc protrusions, but symptoms and findings of an atypical or unusual nature eventually resulted in further diagnostic procedures.[363, 364, 976] Two patients with lumbar spine metastases were subjected to surgical treatment for prolapsed discs. Pain was temporarily relieved in one, but persisted in the other. Postoperatively, a carcinoma of the breast was discovered in one patient, and a carcinoma of the esophagus in the other.[1323]

A single test (really a performance of the Valsalva maneuver) for increasing intraspinal pressure was said to be of more value than were the Aird-Naffziger tests. The patient suspected of having a disc protrusion was instructed to take a deep breath through the mouth, to hold his nostrils closed between the thumb and forefinger, and to continue his attempt to exhale through his nose for several seconds after a "popping" sensation of the eardrums was experienced. The test was to be repeated in the supine, sitting, and standing positions. It was considered to be positive only if low back pain and radicular radiation were evoked or exaggerated.[2783]

The level of cerbrospinal fluid protein was of little aid in diagnosis. Total protein was elevated to 50 to 100 mg.% in over half of the patients with protruded discs. It was suggested that protein elevation was associated with nerve root compression.[364] In patients with massive disc protrusion and compression of the cauda equina, the cerebrospinal fluid protein in each of 21 from whom it was obtained was increased, and varied from 55 to 590 mg.%. In 15 cases it ex-

ceeded 100 mg.%. Three of these patients were found to have manometric blocks. In one case the protein content below the block was 590 mg.%; above the block it was 100 mg.%. [No new information of significance regarding laboratory tests or values of constituents of the cerebrospinal fluid was reported.—Ed.]

Electromyography was effective in determining whether a nerve root was compressed, in localizing the specific root or roots affected, and in differentiating acute infectious neuronitis, infectious polyneuritis, mononeuropathies, myopathies, muscular atrophy, and progressive muscular dystrophies from true root compression of intervertebral disc protrusion. The electromyogram was especially helpful in the diagnosis of lesions which demonstrated minimal lower neuron disease.[693] It was also of value in detecting the malingerer, and as a method of quantitating developing and preëxisting nerve damage. Of 45 consecutive cases of surgically verified protruded lumbar discs, 40 had been accurately localized by electromyograms; 38 had accurately localized myelograms.

Roentgen Examination. Roentgenograms were of value in excluding advanced malignancy of the spine, fractures, spondylolisthesis and other anomalies, infectious lesions, and osteoporosis in the study of patients with suspected disc protrusions.[363, 364, 744, 2600] Severe osteoarthritic changes were difficult to evaluate.[363] [In osteoarthritis of zygapophysial joints, overgrowth of bone and soft tissues at the joint margins may lead to encroachment anteriorly, with narrowing of the intervertebral foramina or canal, and compression of the nerve root. Disc degeneration, with narrowing of the interspace and instability of the apophysial joints, also sometimes causes identical changes. It is often difficult to determine which process causes root compression.—Ed.]

Roentgenograms frequently revealed a list of the lumbar spine, loss of the normal lumbar curve and, in long-standing lesions, narrowing of the vertebral interspaces.[2600, 3334] Narrowing of the lumbosacral interspace (L5-S1), with or without symptoms of disc protrusion, was so common that this finding on a roentgenogram was of little value.[364, 744, 3244] Alignment of the vertebrae on lateral roentgenograms in such instances was important. A fifth lumbar vertebra in line with but separated from the sacrum by a narrow interspace usually functioned as a sacral vertebra, and disc rupture, if present, was likely to lie above this level. However, a narrowed interspace between the fourth and fifth lumbar vertebrae was much more significant, and in one series had correctly indicated the site of disc protrusion in 13 of the 15 instances in which it was observed in the preceding 100 patients operated on for this lesion. Myelography was not used when this was associated with other findings indicative of a disc protrusion at that level.[364] In another series, 19 patients had narrowing of the L4-L5 interspaces, and 17 of these were shown at operation to have disc herniation at this level. Explorations in the other two were negative.[744]

Functional radiography of the lumbar spine (lateral views in maximal ventral and dorsal flexion) gave results similar to those obtained by routine radiography in 384 patients with back pain and sciatica, and in 90 symptom-free patients.[25] [It was difficult to evaluate these data. Comparisons of findings in the same patients were not presented. Results of use in disc herniation localization were apparently speculative.—Ed.]

Adequate roentgen examination of the cervical spine was advised before treatment was undertaken.[1724] Posteroanterior and 45° oblique views of the cervical spine were used to demonstrate the covertebral articulations, the projec-

tion of osteophytes from these joints, and the posterior or apophysial joints causing foraminal narrowing. Extensive roentgenographic changes in the cervical spines of older patients were unusually well demonstrated.[1294] Radiographic findings in cervical spondylosis were classified as (1) narrowing of interspaces, with sclerosis of adjacent vertebral margins, and anterior and/or posterior osteophytes, and (2) evidences of encroachment on the intervertebral foramina by posterior osteophytes. Of 40 patients with cervical spondylosis, only two had normal roentgenographic findings, and they had positive myelograms.[444]

Discography. This procedure yielded positive evidence of disc disease, and was most useful in the patient whose myelogram was negative but whose symptoms had continued to suggest disc protrusion.[191, 1869, 2285, 2363, 3347] Cervical discography was considered to be relatively simple and safe, and it was anticipated that the procedure might have certain advantages over myelography.[586, 2857] The degree of pressure necessary to inject the contrast medium, severity and distribution of pain produced by the injection, pattern of distribution of contrast medium on the discogram, and correlation of these factors with history and physical findings were considered to be important. Little resistance during injection suggested rupture of the annulus fibrosus and posterior spinal ligament. Great resistance suggested an intact disc. Sciatic pain during injection was considered to be suggestive of nerve root compression, but this was not always found. Advantages of discography included use of a nontoxic, rapidly absorbed contrast medium, avoidance of radiculitis and arachnoiditis, and direct visualization of the disc. Disadvantages included the increased time needed for individual disc injection, the possibility of the disc infection, and an occasional severe exacerbation of sciatica.[2363, 3347] Discography too often showed only that discs had degenerated, and did not furnish positive evidence of posterolateral rupture as a cause of sciatic pain.[363] In 68 patients, exploration of 107 discs obtained radiologic and surgical agreement in 98, or 91.6%. In the nine discs on which agreement was not obtained, five false-positive and four false-negative diagnoses had been made. The majority of errors represented inherent deficiencies in the procedure. In another group of 73 patients with low back pain and/or sciatica, discography was not superior to myelography for routine diagnosis of herniation of an intervertebral disc. However, discography was useful when myelography was inconclusive.[2285] [It is impossible from the data given to compare results of discography and myelography in individual cases.—Ed.]

Analysis of clinical findings revealed two neurologic syndromes caused by lumbar discs: the first, resulting from compression of the nerve by the disc, was characterized by numbness, paresthesias, and reflex changes, but without increase in pain on coughing; the second was due to irritation of the nerve by perineural spread of contents of the nucleus pulposus through a disc rupture, and was characterized by exaggeration of pain on coughing, and less reflex and sensory change than with the other type.[3202] In eight patients, protrusions were visualized by discograms and their pain was reproduced at the time of injection of the disc; seven were later subjected to surgery and the disc protrusions were verified.[957]

A technic for cervical discography, utilizing an anterolateral approach to avoid the spinal cord and meninges, was described. From 0.5 to 1.0 ml. of 70% Diodrast was used as the contrast medium. Roentgenographic control was not used. No complications occurred in the 70 patients studied.[2857]

Injection of the intervertebral disc with hydrocortisone and iodopyracet solution allowed immediate evaluation of the condition of the disc, and the nature of the response to hydrocortisone. Thirty-seven of 55 patients (67%) had rapid remission of symptoms after the injection of hydrocortisone. Surgical removal of the involved disc in 16 of the 18 failures showed irreversible changes in the discs.[958]

Myelography. Myelography was a most helpful procedure in localizing the compression level of a nerve root or the cauda equina, and was a necessity in making a definite diagnosis of herniated lumbar disc, even though "a significant percentage" of error accompanied the procedure.[50, 744, 2227, 2363, 2718, 2600] Percentage of error varied a great deal, depending upon the indications for doing the procedure; surgical exploration of the spine was preferred.[2681] When myelography was not used routinely before surgery, a relatively low percentage of correct preoperative myelographic diagnoses was found.[364] Those who always did myelograms on patients seriously suspected of having a disc protrusion had many typical cases in their series and a high percentage of correct myelographic diagnoses.[2718] Myelography demonstrated complete obstruction to the passage of opaque medium in 16 of 18 patients with compression of the cauda equina by prolapsed intervertebral discs.[1570] Myelograms proved to be very effective in demonstrating the transverse ridges on the anterior aspect of the spinal canal in patients with cervical spondylosis.[444] Orthopedic surgeons reported that insurance companies, attorneys, and juries rely too heavily on myelographic evidence of herniated discs, and not sufficiently on clinical findings and histories of this condition.[3334] "As a screening procedure for patients with low back or leg complaints," this practice could not be condoned.[365] True multiple disc protrusions causing root compression were uncommon, and occurred in not more than 5% of patients. This low incidence hardly justified indiscriminate use of the procedure. Minor insignificant myelographic changes were considered to be the most common causes of unjustified surgery.[365]

Treatment of Protruded Discs. Few authors held strong convictions that patients with disc protrusion should always or should never have spinal fusion following removal of disc material. It was agreed in general that conservative management for several weeks or months at the onset was proper.[363, 744, 1724, 1827, 2227, 2599, 2600, 3334] Exceptions were those patients in whom massive lumbar disc protrusion compressed the cord or cauda equina and caused paralysis or paresis of the lower extremities, and sphincter disturbances. These conditions have been considered to be emergencies, and have been given the benefit of immediate surgery.[743, 1570, 2998] The same can be said for protruded thoracic discs with spinal cord compression.[5, 6, 1733]

Eighty to 90% of patients with disc syndrome were satisfactorily relieved of their symptoms by conservative management.[2599, 3334] During an acute attack, rest on a hard bed, heat to the low back, massage, analgesics and traction were the essentials of therapy. Partial flexion of the knees and hips, with flattening of the lower lumbar spine, was often tolerated better than was the supine position. Injection of procaine hydrochloride into spastic muscles was used, as were the relaxants, mephenesin and zoxazolamine;[2227, 2599, 2600, 3334] meprobamate was also used as an adjunct to other treatment.[1140]

Various types of traction applied to the cervical or lumbar spine included the manual, continuous sustained, intermittent sustained, rhythmic, and vertical.

Rhythmic traction served as a manipulative procedure. Sustained traction required the use of a traction couch or table. Vertical traction involved suspension of the patient by means of a broad belt around the lower thorax. His own body weight was utilized as a traction force.[1103, 2265] A specially designed traction couch suspended the patient, face down, with his back in hyperextension.[2071] Mechanical traction which utilized a couch was "an advance in the conservative treatment of the lumbar disc syndrome." Of 100 patients, 74 obtained excellent results, 12 good results, and 12 poor results; two were failures.[2353] Contraindications to traction included (1) lumbago with twinges of pain (as violent pain often followed discontinuance of traction); (2) failure of manipulation (traction was not successful for a day or so after unusuccessful manipulation); and (3) respiratory or heart disease of such type that the patient was unable to tolerate the thoracic harness.[713] Another physical therapy consisted of histamine by ion transfer.[2628] Epidural injection of 50 ml. of a 0.5% procaine hydrochloride solution by means of a lumbar puncture needle through the sacral hiatus was of benefit in very acute low back pain, in sciatica of several months' duration, after failure of manipulation and traction, or for referred coccygodynia.[713] Injection of a solution containing 50 mg. of hydrocortisone into degenerated intervertebral discs resulted in remission in 37 of 55 patients.[958] [Confirmation of this work would be desirable.—Ed.] After acute symptoms had subsided and ambulation had been started, patients learned to guard against situations which might produce an exacerbation of symptoms.[2600] Those with recurrent exacerbations learned to limit their movement, and were sometimes advised to use a Taylor brace for from three to six months as an aid to better posture.[2599]

Ultrasound radiations were directed over the site of suspected pathologic damage and also over areas of referred pain. Ultrasound produced hyperemia, vasodilatation, heat, and tissue destruction of varying degrees, depending upon intensity of energy and duration of treatment.[2628,3074] Two hundred nine cases were treated in a five-year period, and 180 patients (86%) showed complete disappearance of symptoms. The remaining 29 patients (14%) had little or no relief, and eventually had surgical removal of herniated intervertebral discs. Of the 180 patients who had relief of symptoms after ultrasound, 22 had mild recurrences from six to 18 months later, and were again relieved by further therapy. Ultrasound therapy was found to be superior to short wave diathermy in percentage of patients obtaining and maintaining improvement, and in the recurrence rate.[35] [These reported results are impressive. Reports of controlled studies are needed to evaluate these claims.—Ed.]

Manipulative therapy without anesthesia, by physicians or by physical therapists directed by physicians, was recommended provided no contraindications were present. Contraindications included (1) injury to the fourth sacral root, as indicated by (a) bilateral sciatica, (b) referred coccygodynia, (c) paresthesias in the saddle area, perineum, genitals, or rectum, (d) interference with bladder function related to lumbago or sciatica, or (e) impotence; (2) acute lumbago with severe pain elicited by gentle pressure on the lower lumbar spinous processes; and (3) psychoneurosis.[713, 2352]

Lateral cervical disc herniations were treated successfully in 80 to 85% of cases by conservative measures, consisting initially of bed-rest and continuous traction of five to seven pounds on the cervical spine by means of a canvas halter or Sayre's head sling. After from one to 14 days the patient was allowed to be

ambulatory, with the neck moderately supported and immobilized by a collar. Traction was continued during the night. The collar and traction were gradually discontinued over a period of two to three months.[429] The importance of applying cervical traction with approximately 20° of neck flexion was stressed. Traction in line with the body tended to hyperextend the cervical spine and to decrease the long diameters of the intervertebral foramen.[694] Local heat, ultrasonic therapy, gentle massage, intermittent traction, and flexion exercises were other recommended measures.[928, 1724] Meprobamate influenced affect and neuromuscular control, and was recommended in patients with whiplash injuries and the cervical disc syndromes.[1140]

Conservative therapy of cervical spondylosis resulted in improvement of the root symptoms, but aggravated spasticity and weakness of the lower extremities. Limitation of exercise and decrease in heavy work were beneficial. Removal of cord-compressing osteophytes from the anterior wall of the spinal canal was not considered to be advisable. Laminectomy with incision of the dura (four cases), laminectomy alone (nine cases), laminectomy with incision of the dentate ligaments (16 cases), and laminectomy with removal of soft disc material (two cases) were considered to be disappointing as far as return to full function was concerned. Laminectomy with section of the dentate ligaments was recommended when and if conservative therapy failed.[571] Others also favored conservative measures rather than surgical therapy.[444, 3369] A more optimistic attitude was expressed in a report of seven cases treated by laminectomy and section of the dentate ligaments, with improvement or arrest in six.[999] Whiplash injuries were treated conservatively by heat, support, traction, and analgesics. Disc injury was rarely present.[1374, 2070, 2728, 3370]

Thoracic disc protrusion with cord compression was an indication for emergency surgery.[5, 6, 1733] A patient with herniated thoracic disc with spinal cord compression causing paresis of the legs was treated by anterolateral disc fenestration, with disappearance of the symptoms and signs. No attempt to enter the spinal canal or remove the prolapsed disc material was made.[678]

An accurate diagnosis was the key to successful disc surgery. Undue enthusiasm for surgical treatment of minor backache, with or without sciatic radiation, led to useless, harmful surgery and caused surgical therapy of disc protrusion to fall into disrepute in some quarters.[2718] Surgical treatment of lumbar disc protrusion was an elective procedure carried out (1) when the patient continued to have severe pain and disability, with or without a neurologic deficit, after an adequate trial of conservative therapy, or (2) when paresis of the lower extremities or other evidence of cauda equina compression developed.[744, 2599, 2600, 3334] Chordotomy, rhizotomy, and spinal fusion were not indicated when exploration for a herniated lumbar disc was negative.[744] When disc disease was associated with nerve compression in the foramen, decompression by uncapping the intervertebral canal was advocated.[139] Patients with one or more of the following stigmata were considered to be candidates for fusion: (1) hemilaminectomy or total laminectomy performed in removal of the disc, (2) spondylolisthesis, (3) spina bifida, (4) sacralization of a transverse process with evidence of a false joint, (5) marked bony osteophytes in the area, (6) marked marginal sclerosis of the contact bony surfaces just above and below the area, and (7) a loose, unstable fifth lumbar vertebra observed at operation and diagnosed by its excessive motion on instrument pressure. Results of surgical therapy were classified

as excellent to good in 82% of compensation cases, and in 80.8% of noncompensation cases.[2718] Others have stated that more than 95% of properly assessed patients with lumbar disc protrusion, subjected to proper surgery, were improved, to at least some extent, following operation.[2600] The dowel type of interbody fusion, carried out on 94 patients, proved to be a simplified, safe method of performing body-to-body fusions.[3333]

Complications of surgery included wound infections, phlebothrombosis, bladder paralysis, injury to great vessels, and interspace infection. Intractable pain, attributed to nerve root involvement which persisted or recurred after operation, was an indication for another exploration. Second operations were performed in from 5 to 10% of patients who had undergone surgery for disc protrusion. Recurrence or rupture of another disc was often found.[364] At the second operation a previously successful spinal fusion was found to have produced compression of the cauda equina and right fifth lumbar nerve root.[184] Any person with a past, true history of a ruptured intervertebral disc was considered to have a permanent disability, even though he might be symptom-free. The disc healed with scarring, and was potentially weak and likely to be injured again at any time.[3334]

Sciatica

Sciatica was not a diagnostic term but a "medical wastebasket" which, in the broadest sense, included any pain radiating down the back of the leg.[205] It was doubtful that primary neuralgia of the sciatic nerve existed. Pain along the course or in any portion of the sciatic nerve distribution was in all likelihood due to a mechanical disturbance of one of the roots, or to direct involvement of the sciatic nerve itself. Pain of sciatica extended from the low back down the buttocks, and along the posterior aspect of the thigh to the outer half of the calf of the leg and foot. The origin of pain varied according to the nerve root or roots involved. A history of trauma was sometimes elicited. Aggravation of pain by coughing, sneezing, straining, or forward flexion of the spine was characteristic of root pain due to an intraspinal lesion. Neurologic examinations varied from completely negative to loss of deep reflexes, muscle atrophy, and sensory disturbances.[681]

Although sciatica was sometimes due to vertebral, foraminal, intraspinal, pelvic, sacro-iliac, and muscular pathology, the only condition ordinarily given serious consideration in diagnosis was that of herniated lumbar intervertebral disc. Oversimplification of a difficult diagnostic problem resulted. In unselected cases the incidence of herniated disc was believed to be considerably below the 90% found in groups of surgically treated patients with sciatica. Actual incidence was difficult to determine, as patients with back pain but without sciatica were not excluded, and most reports dealt only with hospitalized patients. The actual incidence of a herniated disc as a cause of sciatica was probably less than 50%.[50]

Sciatica was again considered to be of two types, differentiated on the basis of tests used to determine nerve root compression. The first type was termed "reflex"[124] or idiopathic[2892] sciatica, and represented the root compression syndrome often associated with sensory phenomena and/or reflex changes. Most of these were due to protrusion of a nucleus pulposus with compression of

a nerve root. Several tests which determined compression of the sciatic nerve roots were described in detail. All were based on the fact that traction on the sciatic nerve caused increased compression of the nerve root as it turned or bent around the compressing mass. These signs were classified as "traction signs of compression of sciatic nerve roots," and were arranged in order of increasing specificity as follows: (1) straight leg raising test of Lasègue (not a specific test, and positive in a number of conditions); (2) dorsiflexion test of Fajersztaju (a refinement of the previous test); (3) posterior tibial test of Crom (pressure on the posterior tibial nerve in the popliteal fossa placing traction on the sciatic nerve [much like the bow-string test described in the Twelfth Rheumatism Review.—Ed.], and more specific for reflex pain because without major sources of false-positive responses); (4) well leg raising test of Fajersztaju (recently resurrected from medical archives); (5) Steindler test (injection of procaine hydrochloride into painful or "trigger" areas, demonstrating unrelieved sciatic pain to be truly "reflex" in type).[124]

The second type, or "referred"[124] or symptomatic[2892] sciatica, consisted of pain referred from a lesion such as arthritis of the sacro-iliac or apophysial joints in the low back, by way of the sacral plexus, over the distribution of the sciatic nerve. Sensation and reflexes were unaffected. Pain was not aggravated by traction on the sciatic nerve roots by the tests just mentioned.[124]

The "flip sign" in detection of the "simulator" (malingerer) was a modification of the straight leg raising test. The patient was instructed to sit squarely on the examining table with his legs dangling, his back as erect as possible, with his arms at his sides. The examiner placed the open palm of one hand just above the knee of the affected extremity and pressed the thigh down on the table. The other hand held the patient's heel on the affected side. The affected extremity was then gradually extended at the knee. In cases of sciatica due to root compression, extension beyond about 45° resulted in an acute reversal of the lumbar lordosis, and the patient often fell back precipitously.[2124] The "sciatic tension" test, a modification of Crain's "bow-string" test, and several modifications were used to demonstrate nerve root compression. Pressure in the popliteal space, together with traction on the nerve root, was the basic test. A modification of this test, in which the sciatic nerve was placed under tension just short of causing pain, with application of jugular compression, proved to be of value.[765]

Lesions which caused sciatica included neural arch defects of spondylolisthesis, metastatic tumor of the spine, metastatic or primary tumor of the pelvis, infections of the spine, pelvis or hips, bursitis, tendinitis, painful fat nodules, infectious neuritis such as herpes zoster, hip joint disease, and segmental arterial occlusion.[1184] Primary tumors of the sciatic nerve, diabetes mellitus, tabes dorsalis,[681] a narrow spinal canal, sacro-iliac arthritis and ligamentous strain were other reported causes.[2960]

Differential diagnosis of low back, hip and leg pain (including sciatica) in elderly patients was often difficult. The seven most frequently encountered lesions included protruded lumbar discs, diabetic neuritis, peripheral vascular disease, varicosities and phlebitis, malignancy in the pelvis and femur, primary intraspinal tumor, arthritis of the hip, knee or ankle, and gout. Diabetic neuritis often appeared even when the diabetes was well controlled.[2114] Vertebral osteophytosis caused pain with the characteristic sciatic radiation.[255] Sciatic pain without pathologic changes and root compression by the disc at operation were

considered to be indications for "uncapping" the nerve roots of the intervertebral canal, especially the fifth lumbar.[139] Pseudosciatica of fibrositis and myositis was considered to be more common than sciatica of herniated disc, collapsed vertebra, tumor of the root or meninges, pelvic tumors, gluteal abscess, soft tissue tumors or primary neuritis.[1440]

Sciatica accompanied relaxation of the ligaments that supported the inferior margin of the sacro-iliac joint near the site of insertion of the pyriformis muscle.[1289] The sciatic nerve passed below the pyriformis in 87.5% of cases, through it in 12%, and above it in 0.5%. Spasm of this muscle due to painful ligamentous relaxation with involvement of the adjacent sciatic nerve was blamed for the sciatica. Injection of a mild irritant solution (prolotherapy) into the fibers of the relaxed ligament at the site of its insertion into bone was said to stimulate new bone and fibrous tissue production, with permanent strengthening of the "weld" at the fibro-osseous junction.[1289] [No control data, and no specific series of patients with sciatica were presented.—Ed.]

Four cases of meningeal diverticula of sacral nerve roots (perineural cysts), with characteristic myelographic findings, were reported. Sacral pain was in some instances associated with sciatica.[3010] Herniations of fat lobules over the sacrum and the low back were tender when palpated. Pressure on these nodules from any cause resulted in back pain with associated sciatic pain. No sensory or reflex changes were noted.[2760] During exploration for suspected disc protrusion, a loop of the first sacral root which had herniated into the dural sheath of the fifth lumbar root was replaced in the spinal theca, with complete relief of the sciatic pain.[2915] Two patients developed sciatica in previously amputated legs. Symptoms in both instances were due to disc protrusions, and both patients were relieved of pain by removal of the offending discs. At no time was there anything to suggest causalgia or "phantom limb pain."[1718] Cervical spondylosis gave rise to brachialgia in two patients with simultaneous pain in the leg resembling sciatica, and there were findings of a pyramidal tract lesion; complete relief of pain occurred following surgery.[3116] Six patients with tumors of the high thoracic or cervical cord, with sharp, shooting or burning pain referred to a lower extremity and simulating sciatica, were also reported. All were females over 50 years of age. The pain could easily be confused with that caused by a herniated intervertebral disc or an intra- or extraspinal lesion involving the roots of the cauda equina or peripheral portion of the sciatic nerve. However, all had findings of pyramidal tract involvement. Such burning or sharp pain was sometimes confused with incomplete peripheral nerve lesions, vascular disease of an extremity, thalamic lesions or even "functional states." Investigation of such pain states, with involvement of the lower extremities, included myelographic investigation of the lumbar, thoracic, and cervical spinal segments.[2715] Sciatic nerve palsy occurred during delivery, and three femoral nerve palsies developed following gynecologic operations.[19] A rare type of femoral-sciatic neuropathy was reported in two elderly patients with diabetes mellitus of short duration who had asymmetric pain, muscle paresis, and reflex disturbances without loss of sensitivity. Study of one showed involvement of peripheral nerves rather than a myelopathy. Changes in the sciatic and femoral nerves consisted of a patchy demyelinization of nerve fibers, and atrophy of nerve bundles with fibrous replacement and thickening of the walls of the small and medium-sized vessels in the perineural tissue.[2835]

In view of the variety of conditions causing sciatica, uniformity in treatment was not to be expected, and depended upon the cause.[50] In the conservative management of sciatica, an attempt was made to immobilize the lumbar spine as soon and as completely as possible.[2883] Prognosis of conservatively treated sciatica was fairly good, as shown by the results in 300 cases. Review of the results eight to 23 years after therapy found that 52% were completely free of symptoms, and 27% had only occasional mild pain.[2892]

Gout and Gouty Arthritis

Important advances in recent years have increased knowledge of the basic defects in this disease and improved therapeutic programs. It was generally agreed that gout represented a metabolic abnormality in uric acid metabolism which had a definite hereditary background. It had become apparent that several metabolic abnormalities might occur in the organism, producing the same end result, i.e., acute gouty arthritis, bursitis or tendinitis, tophi, and chronic gouty arthritis. It became increasingly apparent that, in primary gout, a single metabolic defect may not explain the consistently increased total body urate. The lack of homogeneity among the gouty population was emphasized by reference to "secondary gout"; even within this category, the predominant pathways of uric acid biosynthesis might differ. Obvious advances had been made in therapy; control of all acute and impending attacks of gouty arthritis could be anticipated. Potent uricosuric agents facilitated management of tophaceous gout; with good renal function, adequate uricosuric effect from one of the several different potent agents could be expected.

Significance. Historical aspects of gout were discussed in a number of reports.[298, 648, 870, 1363, 1679, 1953, 3049, 3050, 3052, 3053, 3221] A unique bibliography reviewed selected publications of Wollaston, Scudmore, Bence Jones, Charcot, Minkowski and others.[298]

Incidence and Age of Onset. The incidence of gout in relation to the abundance or scarcity of dietary fat and protein in ancient and more recent times suggested that the frequency and severity of the disorder had gradually diminished during the last few decades in Europe.[1363] In his Heberden Oration, Brøchner-Mortensen noted: "In Denmark we have fairly good evidence that the incidence of gout was decreasing during the two World Wars but it has now again become fairly common." The incidence ". . . varies considerably from country to country, even within a small area such as Scandinavia. Gout is very common in Denmark and southern Sweden, rare in northern Sweden and Norway, and apparently almost nonexistent in Finland."[392] Failure to recognize the disease in the absence of advanced tophaceous changes was a common professional shortcoming.[3050] [At times it appears that the misdiagnosis is too common.—Ed.] Of 589 individuals referred in one year to a University arthritis clinic, 5.8% (34) had gout,[984] but in a metropolitan orthopedic clinic, in a three and one-half year period, clinical evidence of gout was reported in only 72 (0.7%) of 9,399 new patients.[2584] Gout might appear unexpectedly in any physician's practice.[3052]

Gout was recognized in South America[3053] and in the Negro race, in both Europe[729, 1196, 1414] and the United States,[2574] but "estimates concerning the incidence of a given disease in various racial groups have little meaning without

reference to the population sample from which the experience is drawn and the methods and criteria employed in diagnosis."

The rarity of gout in women was again noted.[175, 392, 984, 2637, 2751] A "high surgical population" could account for an increased incidence in postmenopausal women.[175] The influence of pregnancy and gout upon each other was discussed.[1059] A report of six cases threw doubt upon the special rarity of gout in the Negro female.[2574] [Tophi were definitely present in four and possibly in a fifth individual; in all instances, tophi appeared after the menopause.—Ed.]

It was generally agreed that the first attack of gout usually appeared between the ages of 25 and 60; percentage distribution by age at the first attack was tabulated from the literature for the period 1866 to 1958 in almost 400 individuals.[392] The occurrence of acute gouty arthritis in an 11 year old girl was described.[632] Special features of "juvenile gout" were reviewed.[737, 2721] The first attack of gout developed in individuals past 45 or 60 years,[392, 1915] but ". . . of course, the patient [had] had gout all of his life."[2632]

Tophi. The tophus remained indisputably the most useful clinical sign of gout; demonstration of urates, either by crystallography or by the murexide test, established the diagnosis.[195, 196] Tophi in the helix of the ear or about affected joints occurred in from less than 25%[3047] to 50% or more of patients.[632, 2751] It was generally agreed that they became more frequent as the duration of the disease increased.[3049] Tophi were not found in Frenchmen who had had the disease for less than five years, but occurred in 70% of those who had had gout for more than 20 years.[2751] Of 235 patients free of overt renal damage, 33% exhibited tophi, whereas tophi were present in 71% of patients with renal damage, and one third of the latter group had extensive deposits; after age 50, the incidence of tophi was significantly greater when renal damage was present than when it was absent.[1280] [Both tophi and renal damage from gout represent evidence of more severe gout. Any other significance of this coexistence is not yet established.—Ed.]

It was once again observed that tophi should be looked for in the outer ear, hand, foot, elbow, and knee, in that order.[2751] Gout, unlike R.A., did not cause nodules under the olecranon.[632] [We cannot agree. Subcutaneous olecranon nodules in both diseases may appear identical grossly, but biopsy and microscopic examination are the only sure proof.—Ed.] A solitary, cystlike lesion of the patella, proved by biopsy and laboratory studies to be a tophus, occurred in a patient with gouty arthritis without evidence of tophi elsewhere.[1958]

A patient with tophaceous gout and a proved pure uric acid calculus of the partoid gland was described.[288] Isolated instances of uric acid deposits recovered and identified chemically in atypical areas of the body included the tongue, epiglottis, vocal cords and arytenoid cartilages, the eye, valves of the heart, myocardium, and the corpus cavernosum and prepuce of the penis. Bilateral compression with median neuritis by compression by large urate deposits in and about the carpal tunnels was described;[3224] surgical decompression of the nerve was helpful.[3224] Tophaceous gout in women was uncommon, and was reported for the first time in a premenopausal Negro woman.[632]

Tophi rarely might antedate the onset of acute gouty arthritis.[2751] Their appearance in "juvenile gout" in a 17 year old male with the onset of acute arthritis at age 15,[737] and in a 22 year old male who had experienced the first attack at age 16, was described.[2721]

Incidental Associations. In both the French [2751] and the Danish [392] experience, many gouty patients were overweight (up to 50%); 85% of the French patients followed a sedentary occupation; 18 of 100 were heavy drinkers. In Denmark, bartenders, brewery workers, and salesmen predominated; out of 93, 13 were teetotalers, 21 took one or two bottles of beer a day, 31 had five to 10 bottles, and 17 more than 10 bottles!

Edema of the glottis occurred in a gouty subject and threatened respiratory obstruction; gout was thus considered as a cause of respiratory obstruction.[521] [Proof of the diagnosis of gout was lacking.—Ed.] In an etiologic survey of 100 cases of granulomatous uveitis, 16.3% had elevated blood uric acid values; however, a clinical diagnosis of gout was not made in a single case.[2699] [Caution should be observed in accepting these results, since the method of uric acid determination was not described.—Ed.]

In a review of renal function in 300 patients with gout, of 65 with overt renal disease, two had chronic glomerulonephritis, three had polycystic kidneys, 17 had hypertensive cardiovascular disease, 16 had coronary thrombosis, four had had cerebral thrombosis, and nine had nephrolithiasis with associated pyelonephritis of varying degrees. Of the 235 gouty subjects free of overt renal disease, 27 had or had had nephrolithiasis, 16 had hypertension, 13 had had coronary thrombosis, and two had had cerebral thrombosis.[1280]

The association of gout and diabetes received close study.[48, 176, 1414, 2751, 3267] Of 143 consecutive patients with gout in whom blood sugar levels were done over a period of 12 years, 40 (28%) showed elevation; only one required insulin; there were no differences in clinical features of gouty patients with and without abnormal carbohydrate tolerance.[3267] In 82 ambulatory gouty patients there was a high incidence of abnormal or impaired carbohydrate tolerance, and the fasting blood sugar level was significantly higher in the gouty individuals than in 27 patients with arthritis, suggesting that an intermediary product of nucleoprotein breakdown with diabetogenic properties resulting from the metabolic disorder in gout might be involved; another possibility considered was that gout and diabetes are gene-linked.[1414] In a five-year survey of 50 patients with uric acid calculi, diabetes mellitus was present in approximately 50%.[48] [This combination requires careful exploration and elucidation.—Ed.]

Hyperuricemia was present in 23.4% of 351 patients with peripheral vascular disorders; the degree of involvement seemed to be related to the degree of uric acid elevation; cholesterol levels were also determined.[1765] Gout was associated with coronary artery disease.[1263] [Much more rigid control of laboratory methods will be required before the interpretation of these findings is clear. Similar study will be required to define the incidence of coronary artery disease in patients with gout.—Ed.]

Secondary Gout. Encouraging progress in definition of the clinical and metabolic features of this fascinating group of disorders associated with secondary gout has been achieved through the painstaking investigations by Gutman, Yü, and Weissmann.[1282, 3392] On the basis of metabolic studies, secondary gout was defined as "an acquired complication, particularly of certain hematopoietic disorders in which, incidental to markedly accelerated turnover of nucleic acid related to overproduction of one or another type of blood cells, there is excessive biosynthesis of uric acid and other purines by indirect metabolic pathways involving increased formation and degradation of nucleic acid." [1282] Fea-

tures which determine secondary gout included: (1) association with myeloid metaplasia and polycythemia far too frequent to be due to chance; (2) a conspicuously infrequent history of familial transmission of the gouty trait; (3) the less striking predilection for the male sex, and (4) the more or less unique clinical features, including prolonged acute attacks, rapid development of tophi, urinary calculi, and marked hyperuricemia. Hyperuricemia associated with renal insufficiency, cardiac failure, malignancies, acute febrile illnesses, sepsis, pneumonia, and hemorrhage was not associated with acute gouty arthritis or tophi.[1282, 2937] Moreover, there were individuals with known hyperuricemia, unquestionably due to the gouty trait, who for many years developed either acute gouty arthritis or tophaceous deposits, or never developed either. [For these reasons, the term "secondary gout" should be reserved for the few patients who develop clinically overt gout and/or tophaceous gout secondary to diseases producing hyperuricemia and responding to the same therapeutic measures as employed in primary gout.—Ed.] Blood dyscrasias of short duration did not afford time for the development of secondary gout.[1953] This association, however, was not so infrequent as is usually indicated by the modest number of such cases reported.[287]

Cogent evidence for the presence of distinct metabolic anomalies in secondary and primary gout was obtained by studies of the rate and magnitude of incorporation of glycine-N15 into uric acid. The occurrence of hyperuricemia and/or hyperuricosuria in some cases of polycythemia was attributable to overproduction of uric acid. The predominant route of uric acid biosynthesis did not involve rapid "shunt" metabolic pathways.

The presence or absence of overt secondary gout was not associated with a detectable difference in the rate or magnitude of glycine incorporation; nor, from these curves, could it be determined whether clinically overt gout would develop. The sharp contrast between the rapid peak of glycine-N15 incorporation into uric acid in primary gout and the slow peak in secondary gout indicated, despite the similarities in clinical manifestations and therapeutic responses, that the predominant pathways of uric acid biosynthesis were different and that they had a different pathogenesis. Studies of urinary excretion of purines other than uric acid in both primary and secondary gout revealed, in polycythemia vera, excretion of 8-hydroxy-7-methyl-guanine, demonstrated by glycine-N15 incorporation to be an endogenous metabolite. The miscible body pools, turnover rates, and excretion of uric acid were measured in three leukemic patients by uric acid-2-C14; the pool sizes varied from normal to elevated, but turnover rates were normal, and the per cent recovery of labeled urinary uric acid was normal.[2756]

The urinary excretion of uric acid in patients with leukemia was measured before and in some instances after treatment with cortisone, 6-mercaptopurine, nitrogen mustard, and 1,4-dimethanesulfonyloxybutone (Myleran).[1172, 2659, 3236]

Concomitant gout and lead toxicity were reported in two patients; with deleading, acute gouty arthritis occurred in one.[1953] A detailed clinicopathologic conference described a patient with irradiated polycythemia vera, diabetes, hypertension, gouty arthritis, nephrosis, and compression fractures, in whom the final anatomic diagnosis was myelocytic leukemia.[581] Treatment of the attacks of secondary gout or complicating gouty arthritis was the same as for primary gout. With radiation or chemotherapy,[1916] there was a temporal relation to acute articular gout.[287] The concomitant use of uricosuric agents with active treatment of the primary hematologic disease might result in additional plethora

of nucleic acid end-products and uric acid into the blood, with overloading of the renal excretory mechanism,[195] obstruction of renal tubules and urinary outflow tract with uric acid deposits[1916] or acute uremic episodes.[425, 1172]

Provocative Factors. The patient's history and experience needed to be carefully reviewed to determine what precipitating factors, if any, were applicable to his individual problem and could be minimized or eliminated.[2565, 3054] Factors listed included: food allergy (rarely), fasting or sudden change to a very low caloric diet,[2565] direct trauma, nonarticular infections, emotional distress, blood loss, and surgical operations, and possibly lead intoxication.[1953] Trauma appeared to be a precipitating factor in 11 of 66 patients (16.6%).[2584] After a surgical procedure, the onset of acute gouty arthritis usually occurred within 24 to 36 hours, but might be delayed as long as one week.[175] [Most postoperative attacks of acute gouty arthritis occur from the third to the seventh day.—Ed.] Drugs capable of inducing hyperuricemia and acute gouty arthritis received increased attention; to the list of those cited in the past were added pyrazinamide, chlorothiazide and hydrochlorothiazide. [It is clear that drugs and/or other factors may precipiate an acute flare-up of quiescent gout; whether they can induce or precipitate acute gouty arthritis in an otherwise "nonsusceptible" individual is as yet an unsettled question.—Ed.]

Factor of Heredity. The factors of heredity in gout were redefined.[392, 2721, 2751, 2877, 2938, 2939, 2940, 2945, 3048, 3050, 3052, 3054] The reasonably established knowledge was summarized:[2721] (1) about 25% of relatives of patients with gout had hyperuricemia, the vast majority being males; (2) of those with elevated blood uric acid, only about 10% of the heterozygotes for this factor presented clinical manifestations of gout; (3) hyperuricemia in family members was due to a single autosomal dominant gene; (4) although 95% of patients with overt gout were males, the trait of hyperuricemia was not sex-linked. It was believed that heterozygous women were less likely to have elevated serum urates because of a lower normal blood level and a lessened effect of the abnormal gene in women.

The inherited disposition was reported to be higher in Great Britain (31 to 81%) than in the United States (6 to 18%); although the reason for this difference was not evident, it did not necessarily reflect a true difference in incidence between the two countries. Accurate analysis of the hereditary tendency and the exact mode of transference of the genetic factor awaited more extensive surveys based upon reliable clinical diagnosis, the criteria for which were clearly defined.[2877] [But not always clearly applied.—Ed.]

Nothing new on the effect of age and sex on the blood uric acid levels in normal individuals was reported, but hyperuricemia in gouty families was important because of advances in the clinical management of gout. An elderly woman with typical R.A. with subcutaneous nodules and persistent hyperuricemia had a son and a nephew with hyperuricemia; the latter had typical acute gouty arthritis.[2877] This evidence indicated that the R.A. patient was also a carrier of the genetic trait for gout in a hyperuricemic family.

Pathogenesis of Hyperuricemia. Hyperuricemia was the cardinal feature distinguishing those who possessed the trait of primary gout; in the gouty subject, there was consistently more miscible urate than in normal man.[3376] The hyperuricemia could represent (1) decreased destruction of uric acid, (2) overproduction of uric acid, or (3) abnormality in the excretion of uric acid due to one or more renal defects. Recent information obtained from carefully performed renal clearance studies and from the elegant methods of exploring purine biosynthesis and uric acid metabolism in man and animals could support theoretically responsible factors, but there was no clear-cut explanation applicable to all cases.[3376]

Uricolysis occurred in mammals, including man,[2721, 3376] and, when diminished, could account for the accumulation of urate in some patients with gout;[257, 3175] but uric acid degradation could occur in cells by two enzyme systems, the peroxidase and the cytochrome-cytochrome oxidase. There was evidence that, when purified uricase was injected into normal man and gouty subjects, the same end-product, allantoin, was produced as in lower animals.[1928] [This is obviously a field in which future developments will be awaited with interest.—Ed.] In some but not all patients with primary gout, a metabolic abnormality in the nature of overproduction of uric acid was demonstrated.[1280, 2720, 3175, 3379]

Evidence for and against a specific renal defect in gout remained an area of conflict. This involved the questions of whether uric acid is normally completely filtrable at the glomerulus, what proportion of uric acid is reabsorbed by the tubules (and the enzymatic processes whereby this occurs), and whether, indeed, tubular excretion of uric acid does occur, and whether the gouty subject differs from the normal in these functions.[1672] Even with answers to these questions, there remains sharp disagreement on whether, on the basis of present-day methods, there is a specific abnormality in renal excretion of uric acid. On the basis of clearance technics, Gutman and Yü have concluded that, in the normal response to increased filtrable load, there is no primary, intrinsic anomaly in the gouty kidney; the major anomaly appeared to be prerenal.[1281] Recently, however, evidence has been presented that, in some patients with gout, abnormal renal excretion of uric acid exists and is an important cause of hyperuricemia. It is speculated that, in addition to the overproduction of uric acid demonstrable in some patients, a metabolic defect in gout might affect the plasma urate concentration by (a) the production of a non-urate substance affecting renal excretion of uric acid and resulting in hyperuricemia; (b) the production of uric acid that was bound to protein or differed from the remainder of the plasma uric acid in some other respect, or (c) a metabolic defect affecting the kidneys in some more direct manner (Nugent, C. A. and Tyler, F. A.: J. Clin. Investigation **38**: 1890 [Nov.] 1959). Thus, pathogenesis of gout may be a function of several metabolic abnormalities. [Evidence for tubular elimination of uric acid in a human subject was presented by Praetorium, E. and Kirk, J. E.: J. Lab. and Clin. Med. **35**: 865 [June] 1950). Reference to this study was incorrectly reported in the Twelfth Rheumatism Review (*11*).—Ed.]

In secondary gout incidental to an acquired, markedly accelerated turnover of nucleic acids, related to overproduction of one or another type of blood cells, there was excessive biosynthesis of uric acid and other purines by indirect metabolic pathways.[1282, 3392] Suggested endocrine and allergic causes for gout were still not supported.[1872, 3175]

Pathogenesis of Acute and Chronic Gout. The thesis that metastatic precipitation of uric acid was responsible for acute and chronic gout has been summarized;[2905] bases for rejecting this thesis included these: (1) in chronic tophaceous gout, in which large amounts of urate are deposited, acute inflammatory reaction may be conspicuously lacking; (2) hyperuricemia produced by intravenous introduction of sodium urate into normal and gouty subjects has failed to precipitate acute gouty arthritis; (3) colchicine, which specifically suppresses acute gouty arthritis, is not known to affect the synthesis or excretion of uric acid; (4) probenecid, which does increase elimination of uric acid, does not relieve acute gouty arthritis.[2905] Other purines arising from the disturbed metabolic processes in acute gout might have more irritative properties than uric acid,[2905] but "when the composite syndrome of gout is fairly viewed, in broad perspective, it seems hardly possible to comprehend it as a consequence simply of hyperuricemia. . . ."[1280]

The hypothesis that urate deposition follows upon some primary pathologic alteration of the tissues was not unreasonable. [See The Pathology of Gout, this section.—Ed.] The renal lesions of gout present another area of uncertainty in pathogenesis,[2721] but the obvious relationship between the development of renal damage in gout and the occurrence of tophi was documented;[1280] after age 50, the incidence of tophi was significantly greater when renal damage was present than when it was absent. The acute inflammatory joint disease and disturbance of purine metabolism were apparently dissociable, and the natural occurrence of one phase of the disease without the other—for instance, hyperuricemia in the relatives of gouty patients without clinical gout and, conversely, "colchicine-responsive arthritis resembling gout" in the absence of hyperuricemia—was noted. "One wonders, indeed, whether or not these two aspects of the disease are causally related at all—whether, perhaps, they may not be genetically related."[2721] Despite the possibility of multiple pathogenesis, the resulting clinical manifestations, whether acute gouty arthritis or chronic tophaceous deposit, were very much the same.[1282, 3392]

Laboratory Data. "Urate" (used interchangeably with "uric acid") referred to the anion salt of uric acid, which constitutes the principal form of the degradation product in the body. Technical features of the quantitative analysis of uric acid, especially in blood and urine, were reviewed.[49, 98, 1373, 1407, 2407, 2755, 2949, 3394] As to the inherent though more or less compensating errors of the most reliable colorimetric methods, it was said: ". . . replicable results approximating the 'true' uric acid can be obtained . . . if properly carried out."[3394] Hemolyzed samples needed to be rejected, and examination could not be delayed, since serum uric acid levels declined on standing overnight, and urinary uric acid precipitated out in the cold, particularly when the pH was low. Whole blood was less desirable for measurement of uric acid than was serum or plasma, because of unequal distribution of urates between cells and plasma, and because of the presence of interfering substances in red cells. Drugs affecting the level of uric acid in serum and urine (probenecid, salicylates, phenylbutazone, sulfinpyrazone, zoxazolamine, ACTH, and adrenocortical steroids) needed to be discontinued for from 48 hours[3054] to one week[3394] when nonmedication levels were desired.

With a "direct" colorimetric method [Buchanan, O. H., Block, W. D., and Christman, A. A.: J. Biol. Chem. **157**: 181, 1945.—Ed.], duplicate determinations of uric acid in serum or plasma agreed within 3%; recovery of added uric acid was within ± 5%; checks on urine were at least as close.[3394] In this method, crude uricase removed uric acid by oxidation to allantoin (which does not react with chromogens), thereby permitting correction for non-urate chromogens. However, the quantity of non-urate chromogens in serum or plasma was ordinarily small (equivalent to 0.1 to 0.3 mg.% uric acid), and correction by the uricase procedure was not considered to be necessary.

The average urinary uric acid excretion of normal human subjects on a free diet was reported to be about 700 mg./24 hours, increasing with large purine and protein intake; on a low purine, restricted protein diet, it was 200 to 300 mg./24 hours lower; in 13 normal individuals, the range was 360 to 438 mg./24 hours, with a mean of 416 ± 68 mg.[3394]

Other modifications of the colorimetric method were described,[98] and normal values cited[49, 1625, 2751, 2938] were found to be comparable to those with the spectrophotometric method.[1407] Excellent agreement, on the basis of a protein-free

filtrate, was found between uric acid content of synovial fluid and serum collected simultaneously but over a period of seven weeks; variation of about 25% occurred in plasma uric acid levels.[1625]

The enzymatic method with uricase was highly specific but required an ultraviolet spectrophotometer and a highly purified uricase preparation; normal serum and urinary uric acid values by this method were tabulated.[392, 687] No regular pattern of 24-hour variation could be demonstrated in serum uric acid concentration in normal males on an ordinary diet.[3398] The average uric acid concentration in cerebrospinal fluid was higher in normal men and, when measured simultaneously in plasma, averaged 6% of the plasma concentration.[2433] Measurement of uric acid in biologic fluids by ion-exchange separation and colorimetric or enzymatic spectrophotometry was described.[2755] The serum uric acid level in normal infants was considerably lower than in adults.

Dependable uric acid determinations were of great significance in the diagnosis of gout, and essential in following the response of the patient to uricosuric agents. Sharp differences of opinion were encountered concerning the incidence and persistence of hyperuricemia in primary gout. There were "nonbelievers": ". . . the finding of hyperuricemia is of academic interest but of little diagnostic importance."[1107] To others, ". . . an elevation of the blood uric acid level does not always mean a diagnosis of gout."[196] In approximately 50% of patients the uric acid level was normal in an acute attack,[919, 1717] as a result of a spontaneous uricosuric response at the time of an attack,[175] or became elevated after the attack subsided. A more restricted opinion was that hyperuricemia antedated by many years the first attack of acute gouty arthritis, and persisted between attacks if uricosuric drugs were not given.[1915, 1916, 3394]

Hyperuricemia was reported in about 75% of the "early cases of gout."[392] "It was previously believed that the level was higher before and during the acute attack than in the intervals but I have not been able to confirm this. After five years' duration, hyperuricemia is found in most patients, but normal or only slightly elevated values may sometimes be found even in cases of severe tophaceous gout." [This Committee would only add and stress that the pitfalls in uric acid determinations—and hence evaluation thereof—are many, and point out that, unless the technician is familiar with possible sources of error in the determination, a false or equivocal value may be reported; and unless experience in a laboratory has been consistent, the value of a single determination may be of little diagnostic help. It is, furthermore, of prime importance to be certain that the patient has not received just prior to the test a drug with uricosuric or hyperuricemic properties.—Ed.]

Excretion of urinary uric acid by a child gradually increased with age. Basal urinary uric acid excretion in gouty individuals without renal disease usually was within normal limits or higher.[392, 1280] In 300 subjects with overt gout (average age, 50 years), a mean urinary urate excretion of 497 mg./24 hours (range, 190 to 1520 mg./24 hours) was reported;[1280] the value was within the normal range in 200 (67%), and there were 13 (4.3%) in whom excretion was less than normal. In 87 cases (29%) the excretion exceeded 558 mg., and in 54 cases (18%), it exceeded 628 mg./24 hours. The latter group of 54 patients with unequivocally excessive urate excretion were the "over-excretors." Of these, only four had overt renal damage; their serum urate level tended to be high (a mean of 9.8 mg.%, compared to a mean of 9.0 mg.% in the remaining 246 patients).

Hyperuricemia in Conditions Other Than Gout. It was difficult to define precisely the upper limits of the normal serum uric acid; equivocal or even unequivocal elevations were encountered which could not be related to any apparent disorder.[3394] Because of the association of hyperuricemia and nitrogen retention, the blood urea or nonprotein nitrogen helped to exclude renal insufficiency, but occasionally hyperuricemia preceded urea retention.[3394] Hyperuricemia in patients with R.A. sometimes was attributed to ingestion of small doses of salicylates, which caused retention of uric acid,[3394] but even when salicylates were eliminated, an elevated serum urate occurred in perhaps as high as 10% of patients with typical R.A.[1916]

"Idiopathic" hyperuricemia existed in a definite but unknown incidence; the random occurrence of hyperuricemia in a hospital population was evaluated by a new approach.[1188] Over a seven-year period, uric acid values for a control series ranged between 3.0 and 4.2 mg.%; in this same period, 737 patients had uric acid determinations; of these, 225 showed values greater than 6 mg.%. In this group, 78 gave a classic history of gout; in 26, although gout was diagnosed, the pattern of symptomatology and physical abnormalities was not typical. Thirty-two of the 225 patients had R.A.; the hyperuricemia associated with this diagnosis was predominantly in males, and the initial serum uric acid levels were not so high as in those with gout. Hyperuricemia was often associated with elevation of the hematocrit. Thus, a diagnosis of gout was made in only half of the patients with hyperuricemia; in less than half was the hyperuricemia explained by kidney disease, polycythemia, or a family history of gout.

Hyperuricemia occurred in blood dyscrasias (myeloid metaplasia, primary and secondary polycythemia, chronic granulocytic and acute lymphatic leukemia, pernicious anemia, hemolytic anemia, multiple myeloma), and when there was augmented turnover of nucleic acid. Therapeutic measures associated with acceleration of nucleic acid degradation could result in "fantastic" increases in serum and urinary uric acid. Metabolic studies carried out in an adult with acute leukemia and extensive osteolytic bone disease indicated, in the control period, serum uric acid levels of 6 to 8 mg.%, and urinary uric acid excretion averaging 932 mg./24 hours; during treatment with chemotherapy, there was a temporary increment in urinary uric acid to 1,507 mg.;[3236] other similar reports were noted.[287, 425, 1172, 1953, 2659]

In toxemia of pregnancy, significantly higher plasma uric acid levels and lower urinary uric acid excretion were evident;[714] this was confirmed in studies on metabolism of N^{15} labeled uric acid (based on a precise colorimetric method.)[2726]

With a precise colorimetric method,[49] as well as by the enzymatic spectrophotometric method,[2952] moderate, constant hypouricemia was demonstrated during the first seven months of normal pregnancy; in the eighth and ninth months there was a significant rise, and an unquestionable increase occurred during uncomplicated labor. Uric acid excretion increased with increasing glucose concentration in the pregnant and nonpregnant state.[548] Hypouricemia was described in Fanconi's syndrome and in Wilson's disease where renal tubular absorption was impaired.[3394]

In a series of patients with gout, 32 out of 57 had serum cholesterol levels above 200 mg.%, and four of 100 had moderate glycosuria;[2751] serum calcium was always normal between attacks in 23 patients. The concept of a "gout cycle"

with respect to electrolytes was not confirmed in a metabolic study of six patients during 12 attacks of acute gouty arthritis; adrenocortical activity was well within normal limits.[1871] Serum transaminase levels were elevated at some time during acute attacks of gout, and normal in the interval phase;[3268] there was no apparent correlation with serum uric acid levels. The "glycine load" technic explored differences in amino acid metabolism (chromatographic analyses) in normal individuals and in patients with arthritis, including three with gout. Marked differences were confined almost exclusively to nonessential aminoacids; the rheumatoid and gouty patients showed a more marked and rapid increase in ammonia excretion.[762] Agglutinating activity was not found with the latex fixation test on whole serum or a euglobulin fraction of sera of three patients with gout.[2313]

Mechanism of Renal Excretion of Uric Acid. The renal mechanism for handling urate generally consisted of glomerular filtration, followed by partial tubular absorption.[1280, 1281, 3380] In normal man, plasma urate was generally 90 to 100% filtrable (i.e., completely ultrafiltrable) at the glomerulus; 90 to 95% of the filtered urate was reabsorbed (presumably in the proximal convolutions) by the tubule, and the urate excreted in the urine represented that 5 to 10% of the filtered load which had escaped reabsorption.[1281] Although not identified, presumably the tubular transport mechanisms for urate reabsorption were "actively" enzymatic. The maximal capacity of urate reabsorption was limited (probably with a Tm in the order of 15 mg./urate/min. per 1.73M^2); the magnitude of this rate as defined, however, was such that it was almost never saturated under physiologic conditions.

The plasma urate in gout also was completely filtrable. The filtration rate was relatively well maintained,[1281] and, as in normal man, 5 to 10% of the filtered urate escaped tubular reabsorption; the level of Tm in gout was not examined.[392] With elevation of plasma urate and an essentially normal filtration rate, the filtered urate load was abnormally large (mean of 10.1 mg./min. was about 50% above normal; in some cases it was more than twice the normal mean). The increased filtered urate load proportionately increased tubular capacity for urate reabsorption without, however, reaching the saturation point, indicating excessive tubular reabsorption of urate beyond that of the normal response to increased filtered load.[1281] On this basis, there was no evidence of intrinsic tubular defect in the kidney of the individual with gout. In contrast to the regular relationship of reabsorbed urate to filtered urate, the quantity of urate excreted in the urine in gout was quite independent of the rate at which urate was filtered at the glomerulus. Thus, "an unchanged or normal urate clearance in an individual with elevated plasma content of urate indicates an increase in the actual amount of urate excreted."[1280]

There was renewed emphasis on the possibility that abnormal renal excretion might play a role in causing the hyperuricemia of some gouty patients. A functional disturbance of uric acid transport by the kidney was reëmphasized[3075] and was attacked.[2969] Processes involved in the mechanism of uric acid excretion included ultrafiltration, passive diffusion, secretion, and reabsorption; kidneys were not the sole excretory organs for uric acid, since some was excreted in sweat and in the gastrointestinal tract.[392]

In correlation studies of renal function the serum uric acid increased more slowly than did blood urea and creatinine; in general, however, as an index of renal insufficiency, serum uric acid was no more sensitive than nonprotein nitrogen, serum urea or creatinine, and uric acid clearance no more sensitive than urea and creatinine clearances.[1634]

Pathology. Pathologic changes at autopsy were described in 11 cases collected over a period of seven years; one of these was conspicuous for heterotopic calcification within tophi; despite careful search, urate deposition within blood vessels could not be demonstrated.[1891] Chemical analyses of various constituents of tophi were carried out;[1820] x-ray diffraction and chemical description of crystalline uric acid from a tophus were reported upon.[288]

The tophus characteristically consisted of a multicentric deposit of urate crystals and an intercrystalline matrix, together with the foreign-body granuloma that it has evoked; the crystals were acicular and arranged radially into small, compact clusters; an early stage in tophus formation could be represented by the presence of individual urate crystals.[2721, 2905] The crystals were generally believed to be sodium acid urate, but crystallographic studies suggested that they were uric acid rather than the salt.[288] In articular deposits, granular or amorphous urates were also described; conversion in tissue fixation was a possibility.

The manner in which inflammation is evoked was also obscure. It was suggested that urates were deposited as isolated crystals in articular tissues during acute gouty episodes,[392, 3411] or that deposition of urate in joints preceded clinical symptoms,[392] but crystals of urate could not be demonstrated in an initial attack of acute gout.[3175] [Recently a technic to demonstrate uric acid crystals in sediment of joint fluid was described by Hollander and associates. This could be helpful in the differential diagnosis of acute monarticular arthritis.—Ed.]

The slow rate of development of the tophus or local altered tissue reactivity explained the lack of evidence of acute inflammation in the insidiously developing tophus. The state of the joint in intervals between episodes of acute attacks of gout and the development of the chronic tophaceous deposits was not yet documented anatomically. [All of us must assume an obligation to correct this deficiency. Since the crystals of the tophus are quite water-soluble, it is necessary to reëmphasize that tissues be preserved in nonaqueous fixatives in order to demonstrate urates in histologic sections. It is not known definitely whether urates that may have deposited in the acute attack persist in the tissues or undergo resorption.—Ed.]

Isotopic studies demonstrated that substantial quantities of urate could be present in the tissues and not cause symptoms or give evidence of their presence in roentgenographic or physical examination. In a 54 year old man who, seven years before death, had the first of two definite acute attacks of gout in a big toe, hyperuricemia was definitely established to a level of 7.6 mg.%, although terminally, multiple determinations were below 5 mg.%. X-rays revealed no punched-out lesions of the toe; there was some increased radiolucency. On section, no tophaceous lesions or urate crystals in the tissues were evident.[2905]

In chronic articular gouty arthritis, urate crystals were predominantly deposited radially in the superficial portions of the articular cartilage, and in the synovial and capsular tissues, as well as the periarticular tissues, tendons, and subchondral bone marrow. Unlike the other soft tissue deposits, tophus formation was not a feature of the nonspecific degenerative changes of the articular cartilage; punched-out bony lesions represented marrow tophus deposits which, in most instances, communicated with the urate crusts on the articular surface through osteoarthritic defects in articular cartilage.[2905]

Urate deposits in apposition to bony trabeculae inhibited osteoblastic activity; as bone was resorbed, it was not replaced. Since bone was capable of regeneration, it was possible that normal bone architecture could be restored with ap-

propriate therapy for gout. Urate deposits were seen in the marrow spaces of vertebral bodies, and the sternoclavicular joint was grossly involved in three of four cases in which this joint was examined, but sacro-iliac joints were involved only infrequently;[2905] a tophus from a sacro-iliac joint was described.[1891]

Diagnostic difficulties in distinguishing gout were described.[1820, 2905] In this study, five patients previously considered to have R.A. with persistent or intermittent hyperuricemia were shown by biopsy of the synovial membrane of the knee to have tophaceous deposits. [These observations point out the need for caution in any consideration of the frequency of the coexistence of gout and rheumatoid arthritis.—Ed.]

Functional Status of the Kidney in Progressive Stages of Gout. This subject was critically related to the essential question of whether the hyperuricemia of gout is attributable to an inherent renal defect, specifically of urate excretion, or to overproduction of urate, in which impairment of renal function may be ascribed to the effects of the metabolic defect.[1280, 1281, 2751, 3175, 3380]

Based on performance of standard renal clearance technics in approximately 160 patients with gout, glomerular filtration rate (C_{Inulin}), renal plasma flow (C_{PAH}) and maximal tubular excretory capacity (T_{MPAH}) were, for the most part, consonant with values in normal subjects of equivalent age; impairment of hemodynamics, particularly of C_{PAH}, however, was not infrequent, particularly in those of advanced age or with overt renal disease. In most instances, determinations of urinary urate excretion gave values within the normal range. In a significant minority (18%), however, urinary urate excretion was unequivocally in excess of the limits of normal variation.[1280, 1281]

In these studies,[1280, 1281] excretion of urate was expressed as the filtered urate load (the product of the glomerular filtration rate and the plasma urate concentration). The substantial elevation of plasma urate in these patients, combined with a relatively minor decline in glomerular filtration rate, resulted in a general increase in the filtered urate load. The presumptive tubular reabsorption of urate was correspondingly increased but, as far as could be determined, not disproportionately so, e.g., all but 5 to 10% was reabsorbed. Thus, by clearance technics, essentially normal renal function was found to exist in most gouty subjects, evidence for a primary, intrinsic renal anomaly in gout was not discovered, and the major abnormality appeared to be "prerenal," since the filtered urate load was apt to be excessive.

The normal behavior of the tubular system in conserving filtered urate contributed to and perpetuated the expanded miscible pool in the gouty patient.[503] However, the question is raised whether the quantities of urate excreted per 24 hours were normal only because the plasma urate level in the gouty patient is elevated.

Routine urinalysis, a concentration test, phenolsulfonphthalein excretion test, and blood nonprotein nitrogen determination in 65 of 300 patients (mostly in the older age groups) gave evidence of overt renal disease.[1280, 1281] Of these, two had chronic glomerular nephritis, three had polycystic kidneys, 17 had hypertension, 13 had had coronary thrombosis, and two had had cerebral thrombosis. With advancing years and systemic vascular disease, glomerular filtration rate progressively declined. With deterioration of renal function, the daily output of urate declined, and secondary renal retention of urate became apparent and was apt to progress; in some, this could be clearly related to overt renal damage.

In the gouty subject whose urinary urate excretion was low, superimposed renal damage was of critical significance. [The relationship of renal damage to the development of tophi is discussed above in the Section on Tophi.—Ed.]

The possibility that hyperuricemia itself acts as a nephrotoxin, with prolonged and excessive excretion of uric acid leading to secondary renal damage, was considered.[2721] Hypertension and vascular sclerosis, especially nephrosclerosis, occurred as a part of a constitutional diathesis, of which gout was a component part.[3380] [This so far has been hard to prove.—Ed.] At autopsy, uremia was found to be the primary cause of death in five of 11 gouty patients; another five succumbed to coronary thrombosis, congestive heart failure or intracranial hemorrhage.[1891]

Morphology of Renal Disease in Gout. Comprehensive discussions appeared,[515, 981, 982, 1676, 1891, 2721, 2905, 3380] but "there is a relative paucity of information about the pathologic alterations of the kidney in gout." Features of special interest included (1) the possible renal origin of gout, (2) the frequent renal insufficiency of late gout, (3) the undetermined origin of hypertensive and arteriosclerotic vascular disease to which the gouty subject is prone, and (4) the occurrence of a specific anatomic renal lesion.[2905] Although urate crystal nephrosis was undoubtedly present in a large number of patients (64 of 80 collected cases), it was often of limited proportions. The urate crystals were commonly seen in the interstices of the pyramid despite their probable origin within the tubular lumen. The renal lesions in the majority of patients with long-standing gout were generally a late finding, relatively benign, and not an explanation for the associated hyperuricemia.[2905]

In a review of the pathology sections from 20 patients with gout, it was found that 17 had gouty nephrosis, two had severe gouty nephrosis, four had pyelonephritis, 16 had arteriolar sclerosis, five had arteriolar nephrosclerosis, and none had glomerular nephritis. Up to a certain point, the frequency of arteriolar sclerosis could be accounted for by the age at which the patient came to necropsy; chronic pyelonephritis could also be a contributing factor. Aside from these mechanisms, gout could in "some other special manner" predispose to arteriosclerosis. [This has not been elucidated.—Ed.]

The term "primary renal gout" was employed for the renal disease in persons possessing the gouty trait (e.g., hyperuricemia) but not typical clinical gout; two distinct types of this phenomenon were discussed.[3380] The first of these was urate nephrolithiasis. Urate calculi occurred in approximately 15% of patients with clinical gout but not clinical articular gout. The second type included typical gouty kidneys with no clinical history or other pathologic findings of gout. Primary renal gout was more common than is usually recognized, and it could be suspected whenever hyperuricemia was out of proportion to the degree of renal impairment in patients in whom a completely adequate cause for the renal disease was not apparent. The suspicion would be enhanced by the finding of symptomatic hyperuricemia among family members. With the feasibility of renal biopsy, new information could be anticipated.[3380]

"The paucity of articles in current literature regarding uric acid calculi bears no relationship to their occurrence in the practice of urology."[48]

Patients with pure uric acid calculi and normal blood uric acid were more usual than were those with elevated blood uric acid determinations.

Stones composed of pure uric acid comprised 7% of all calculi; those of urates mixed with phosphate or oxalate comprised another 5%. "Showers of uric acid crystals in the urine may give acute renal colic and hematuria. These crystals are present only in an acid urine and remain in solution in an alkaline urine."[560] The radiolucent nature of uric acid calculi was noted.[919] Uric acid stones serve as a nidus for the formation of radiopaque calcium stones.[982] The incidence of uric acid stones in patients with lymphomas and leukemia was reviewed.[424, 1172, 2659] Spontaneous dissolution was noted to be apparently rare.[48, 246, 981, 982, 1676]

Clinical gout occurring in patients with preëxisting renal disease raised the question of whether renal insufficiency could give rise to true secondary gout.[3380] "One would question whether renal retention of urate would precipitate acute gout in a person not genetically endowed with gouty trait, when urate infusions will not do so even in the gouty person," but it was possible that latent gout could be activated by renal insufficiency. An observation by Magnus-Levy in 1910 was pertinent, namely, that ". . . in many autopsies of uremics, concretions are found in the joints without any history that the patient had ever suffered from primary gout. This observation appears to have escaped most pathologists and warrants confirmation."[2905]

Prognosis

Little was added to the remarks made concerning prognosis in the Twelfth Rheumatism Review. "Juvenile" gout was compared to juvenile diabetes in severity and difficulty of management.[2721, 2877] When the onset of symptoms was before the age of 30 years, the speed of development or rate of progression was likely to be greater than in persons in whom the onset was at a later age.[919]

Diagnosis

The diagnosis of gouty arthritis presented an interesting challenge to the physician; it ". . . should be made promptly, even at the time of the first attack in most instances."[1916] "Our first problem is to teach alertness by the physician, irrespective of the branch of the profession, of the possibility of gout's being responsible for any acute articular disturbance."[1916] A correct diagnosis from the start was made in 63 of 100 patients.[2751] Criteria for the diagnosis of acute gouty arthritis were reviewed.[175, 3051]

Although the acute attack characteristically was sudden in onset, subacute or even insidious onset was observed.[3051] Clinical patterns of involvement of various joints were described.[1916] Premonitory symptoms of burning, tingling, and warmth some hours before the onset of the acute attack in 60 of 95 patients were the "joint warning sign." "The presence of this symptom suggests that the phenomenon of acute gout comes into play before the acute pain begins. Since the first warning of gout should be the signal for prompt institution of therapy, these signs might well be needed to abort or minimize an acute and incapacitating attack."[3266] Seventy of 100 patients were warned by local symptoms;[2751] the premonitory aura also included feelings of unusual well-being, depression, capricious appetite or vague generalized discomfort.[3363] Dilatation of the superficial veins about the affected joint accompanied the swelling and sometimes actually preceded the attack.[2751] Tophi antedated the first attack in about 2% of cases.[2751] Other atypical symptomatology and findings, including the occurrence of wide-

spread ankylosis simulating rheumatoid disease, onset in childhood, gouty nephritis preceding arthritis, coexistence of gout and rheumatoid arthritis in the same patient, and the rapid development of x-ray changes, were discussed.[1188] There was a wide variation in the mode of onset, course, and, pathologic changes in three patients with gouty nephropathy.[982]

It was "not surprising" that renal lithiasis, benign hypertension, and transient albuminuria might precede the first attack; in nine of 100 patients, signs of renal calculus, renal colic or dysuria with a reddish sediment in the urine preceded the gouty attack.[3051]

Differential Diagnosis. In the young male particularly, acute rheumatic fever might simulate acute gouty arthritis, as might traumatic arthritis.[1916, 3051] In post-traumatic arthritis the symptoms appeared immediately after trauma, were localized to the area of trauma, and did not respond to colchicine.[632, 633] Rheumatoid arthritis and osteoarthritis were not associated with overwhelming acute symptoms, but an episodic type of onset in the former disease might defy immediate differentiation from acute gouty arthritis; this was illustrated by case reports.[632, 1188, 1232] Thrombophlebitis,[175, 1498,] acute cellulitis and infectious arthritis also needed to be distinguished promptly.[2181]

Clinical manifestations of recurrent acute arthritis and chronic tophaceous disease in primary and secondary gout were nearly identical.

The therapeutic response to colchicine was as good as any other criteria for the diagnosis of gout, but inadequate dosages provided little symptomatic relief, and might give misleading information.[3052] Use of phenylbutazone for this purpose was described.[1221, 3124, 3325] [However, this drug, as well as salicylates, corticosteroids, and corticotropin, lacks the specificity characteristic of colchicine.—Ed.] In certain circumstances, biopsy of a "nodule," or synovial needle biopsy, or examination of the joint fluid for urates, was helpful.[2877, 3411] The chemical as well as histologic identification of urate for diagnosis was old-fashioned.[2751]

The classic radiographic appearance of tophaceous gout was again described;[2916, 3053] improvement in detail by a magnification technic was described and beautifully illustrated.[3047, 3052, 3053] In the feet of 104 patients with unequivocal gout, there was a similarity between clinical stage of the disease and degree of articular involvement; this appeared to be related to age of onset of the initial articular disturbance and degree of uric acid disturbance. Observation of the characteristic "punched-out areas" demanded reappraisal of the notion[176] that the bone had been destroyed in these locations, since experience indicated that the bony architecture and contour might be restored after adequate modern therapy. This suggested that bone in some cases was merely considerably decalcified and replaced by relatively radiolucent tophaceous material. Gout was the cause of an isolated circumscribed patellar cyst observed roentgenographically.[1958] The similarity of radiographic findings in gout to those in epidermoid cysts of phalanges,[1674] and again to those in Kaposi's sarcoma,[729] was noted.

Terminology and Course. "Classic" (or primary or familial) gout was an inborn (or intrinsic) error of purine metabolism, characterized by an increased concentration of uric acid in the blood and body fluids, and clinically manifested by attacks of acute arthritis.[2877] After the onset of an acute attack of joint inflammation, there were intervals or intercritical periods of complete freedom from joint symptoms, also called the "prophylactic periods."[3051] Chronic gouty arthritis was characterized by low

grade joint pain, deformities, and subcutaneous and bony urate deposits (tophi), and resulted after years of recurrent acute episodes of joint inflammation.[2877]

Ambiguities in the definition of gout, particularly of secondary gout, were emphasized.[2203, 3392] The presence of hyperuricemia and/or hyperuricosuria in association with hematopoietic and related disorders did not of itself justify the diagnosis of secondary gout. This diagnosis was reserved for the relatively few patients with hematopoietic disorders who gave a history of acute gouty arthritis, or perhaps exhibited tophaceous deposits. Such a restriction of diagnostic criteria would not apply in primary gout, and admittedly was not altogether satisfactory in secondary gout. There were, in addition, discrepancies between the magnitude of uric acid biosynthesis and the presence or absence of clinically overt gout which further pointed up these ambiguities. A gouty patient's relative with known hyperuricemia, but who had never experienced an acute attack of gout, possessed "the gouty trait," or had "larval gout,"[2877] or the "gouty diathesis," or "metabolic gout"; [2978] the latter was synonymous with primary or familial gout.[3051]

Treatment

The premise of "complete control" as the therapeutic goal in gout [174, 175, 176] was developed at some length in the Twelfth Review; "this optimistic outlook depends first upon the physician's knowledge of the therapeutic measures available and second upon the patient's willingness to submit to uninterrupted lifetime therapy." [2881] ". . . Advances in the methods of treatment of gout permit effective control of the acute attacks and offer real hope that the advanced stages and late complications can be prevented." [2559] Only many years of experience in the use of these agents would provide the answer to whether complications of gout would be prevented.[195]

Acute Attacks. *General Measures.* Salicylates and cinchophen lacked specificity in acute gout.[176, 2751] Experience indicated that once the acute pain was relieved, a rested joint tended to be uncomfortable. This seemed to explain the common observation of protracted pain in the wrist after an attack of gout, for this joint can so easily be kept at rest, defeating the need for early use.[174, 176] [Rest until inflammation has cleared is still an essential part of treatment.—Ed.] If a patient with acute gout failed to respond to adequate therapy, some other factor had to be considered. Infection and other causes of stress were important among such possible factors; daily use of penicillin was observed to prolong an attack.[176, 1704]

Colchicine. Since the pathogenesis of acute gouty arthritis was incompletely understood, treatment remained empiric.[2721] Criteria for use of new agents in acute gout were listed.[3325] In general, however, with early and vigorous treatment, acute gouty arthritis presented no major therapeutic problem.[195]

Reviews of the use of oral colchicine appeared,[195, 196, 392, 919, 1107, 1704, 1717, 2565, 2721, 2881, 2937, 3052, 3158] but very little new was added. Crystalline colchicine was available as a tablet containing 0.5 mg. or 0.6 mg., but "why there should be two preparations of similar strength in general use [was] impossible . . . to understand." Precautions necessary to guard against therapeutic failure were stressed,[195] including prompt use with the appearance of prodromal symptoms.[2565, 2721] With early treatment, less than 5% of severe attacks failed to respond to the first full course, or required either a second course or some other agent.[1704, 2751] In about 25% of attacks, however, in spite of full amounts of colchicine, swelling and pain of greater or less degree persisted, sometimes for weeks; the

new agents were best reserved for this group of patients.[195] Some patients could not tolerate therapeutic doses of colchicine; "they think that the cure is worse than the disease and so the usefulness of the drug is limited."[2937]

Intravenous administration of colchicine was described;[175, 196, 1107, 2565, 2721, 2751, 2881] its action was quicker than that of oral colchicine, and in most instances terminated the attack before inducing gastrointestinal symptoms;[2721] its special suitability for postoperative attacks of gouty arthritis was stressed.[175, 2881] However, extensive experience to establish the superiority of the intravenous route of colchicine over oral therapy was not available.[195] Irritating effects on the vein at the site of injection,[3051] and use of the intravenous preparation for intra-articular injection, were described; despite use of the latter method in four patients, the symptoms progressed during the treatment, and one of the patients became definitely worse.[1872]

The side-effects of colchicine[195, 392, 2559] included gastroenteritis and intestinal bleeding,[196, 2752] hypersensitivity reactions[195] and dermatitis[1464] associated with its prolonged administration.

For postoperative acute gouty arthritis, the choice of therapy included various routes of administration and different drugs: oral colchicine, intramuscular, long-acting ACTH, intravenous colchicine, oral phenylbutazone, or intra-articular hydrocortisone. When these measures seemed contraindicated, relief was obtained by the intravenous administration of 500 ml. of 20% glucose.[175, 176]

Esters of colchicine were developed with the hope that they might be better tolerated and more effective than colchicine.[176, 195, 196, 618, 1553, 1872, 2141, 2881] An analogue, desacetylmethylcolchicine, was discussed in the Twelfth Review; since then, additional clinical experience has been reported;[618, 2261] in eight of 26 patients, improvement was unsatisfactory. Unfortunately, the toxicity of this preparation made it unacceptable for routine use; the development of delayed alopecia,[618, 2141, 2261, 3269] rash,[618, 2775] and serious hematologic toxicity in the form of transitory anemia and agranulocytosis were reported.[2261, 2775, 3269] [The single advantage offered by desacetylmethylcolchicine is its relative freedom from gastrointestinal side-effects, but the troublesome though temporary diarrhea often associated with colchicine is of far less consequence than the potential risk of bone marrow toxicity inherent in this analogue.—Ed.]

Phenylbutazone. Additional studies confirmed the effectiveness of this drug in acute gouty arthritis;[175, 176, 195, 196, 392, 1221, 1603, 1704, 2010, 2051, 2565, 2721, 2751, 3124, 3325] [Most of us agree that this drug should be reserved for those patients with acute attacks of gout requiring short-term administration. It can be especially useful for patients intolerant or unresponsive to colchicine.—Ed.] In particular, with this agent, early subjective relief of pain, sometimes within four to five hours, often preceded objective resolution of other signs of inflammation.[3325] Relief was obtained most easily with relatively large initial doses, which correlated with relatively low but constant serum drug levels. The "near-specificity" of this agent in acute gout served as a useful diagnostic test.[411, 3124] Acute gouty arthritis responded more dramatically and more consistently to phenylbutazone therapy than did any other rheumatic disorder; the 95% response was superior to results from oral colchicine.[1221] Phenylbutazone was administered by rectal suppository or by intramuscular, intravenous, or intra-articular injection.[195, 2010, 2751] Side-effects were again summarized;[195, 2751] when given for short periods, these were rare.[1704] Unfavorable reactions to phenylbutazone were not apt to occur

until after from seven to 10 days of administration; the interval between the first and twelfth weeks was the critical period.[1221] Careful review of the toxic manifestations and their relation to duration of therapy and total dosage has been presented.[195] [See also Section on R.A. regarding this drug.—Ed.]

Steroid Therapy. It was generally agreed [176, 392, 1704, 1717, 1915, 2565, 2721, 2751, 2881, 2905, 2937, 3050, 3176] that corticosteroids and corticotropin were of limited value in acute gouty arthritis, and that ACTH was superior to newer synthetic corticosteroids. Under special circumstances, corticotropin [176] in combination with maintenance doses of colchicine satisfactorily relieved acute gout within a few hours; the relative merits of long-acting intramuscular preparations, in a gelatin vehicle, or aqueous solutions, and intravenous administration, were discussed.[2565] The corticosteroids (cortisone, hydrocortisone, and their synthetic analogues) were at times useful in patients who did not respond well to colchicine or phenylbutazone, and in whom the use of corticotropin was not practical. In acute cases of gout, particularly if protracted, combined treatment was preferred to a single therapeutic approach; this included the use of oral or intravenous colchicine, or both, a sizable dose of ACTH, and injection of an involved joint or bursa with hydrocortisone.[176, 2721] [Fortunately, treatment of this extent is usually not necessary.—Ed.] Prompt use of steroids in the postoperative attack of gout might be especially helpful.[175] It was reiterated that the favorable action of steroids might be followed by new attacks, and that this recurrence could sometimes be prevented by giving colchicine or phenylbutazone concurrently.

Intercritical Period. Therapy for the intercritical period depended upon the frequency of attacks, unusual work load, or other precipitating factors.[196] Prophylactic daily doses of colchicine were popular and practical for the individual prone to several attacks of gout a year. [A scientific rationale for prophylactic use of colchicine, alone or in combination with uricosuric drugs, has not been clarified. —Ed.] Several investigators have expressed their confidence in the prophylactic value of maintenance colchicine alone,[196, 2565, 2937] or of probenecid alone.[2881] Some investigators expressed themselves as being sigularly unimpressed by the prophylactic value of maintenance colchicine alone; [176, 2881] others expressed doubt of the prophylactic effect of a uricosuric agent in effectively reducing the frequency of attacks.[196, 1221]

In general, phenylbutazone was used cautiously on a maintenance basis; [195, 392, 1704] only one investigator [2751] had had extensive experience with this form of use, although some [2010, 2881, 3387] noted it to be valuable in the later, chronic stages of gout, where complete remission between attacks was not occurring.

Treatment of Chronic Gouty Arthritis or Tophaceous Gout

Chronic gouty arthritis, or tophaceous gout, was distinguished by the presence of tophi and low grade arthritis, but acute attacks of inflammation in joints and bursae might be superimposed upon the chronic joint disease. Therapy [2881] in these circumstances was aimed at controlling the acute flare-ups, reducing stiffness and low grade aching pain, decreasing the size of existing tophi, and preventing the development of new tophi.[2881] Effective therapy for the acute episodes was the same as for acute or pretophaceous gouty arthritis, although if the attack had persisted for some time, more intensive treatment might be required.

Dietary Measures. It was stated again that the diet should be balanced with moderate allowance of protein and fat, and should avoid high purine foods. When patients were overweight, reduction to normal weight and maintenance of normal weight were important aspects of dietary treatment. However, rigid restriction of purine and protein intake was not necessary for the majority of patients with mild degrees of gout. In severe or advanced cases, restriction of purine intake and limitation of protein to 50 to 75 gm. daily, if possible in the form of plant and dairy products, might be indicated.[176, 195, 196, 1704, 2566, 2721]

The effect of war-time dietary restriction on the gouty population was reported from Denmark,[392] England,[888] and France,[2751] where a low-calorie diet was extremely efficacious in 30 of 46 cases. It was difficult to detect which of the imposed dietary or other restrictions were chiefly responsible.[2751]

Uricosuric Drugs

Probenecid. Many general comments concerning probenecid were applicable to other uricosuric agents (cinchophen, phenylbutazone, salicylates, sulfinpyrazone and thiophenylpyrazolidine.[128, 174, 176, 195, 246, 380, 714, 982, 1221, 1281, 1542, 1705, 2301, 2518, 2721, 2830, 2881, 2978, 3054, 3057, 3380] Enhancement of urinary acid excretion associated with appropriate dosages was generally attributed to suppression of tubular reabsorption of urate.[1281] In low dosage, these agents could bring about paradoxic retention of uric acid without any change in filtration rate or filtrability of plasma urate. It was conceivable that they first enhanced and then suppressed one or more mechanisms for urate tubular reabsorption; it was also possible that, in low dosage, they inhibited tubular excretion of urate and, in larger dosage, also inhibited the tubular transport system responsible for reabsorption of urate.[1281] The degree and duration of uricosuria depended upon a number of factors, including plasma urate concentration, purine and fat content of the diet, size of the readily miscible urate pool, rate of endogenous urate production, presence or absence of solid urate deposits, integrity of renal function, and susceptibility to renal calculi.[2721, 2830] The pharmocologic control of renal uric acid excretion included hormonal effects, both physiologic and those induced by therapeutic agents.[2721]

Regulation of dosage was aimed at achieving a 50 to 100% increase in daily urinary urate excretion and lowering of the serum urate level to normal; in the presence of well functioning kidneys, an adequate uricosuric effect with a potent agent was usually accomplished.[176] In 95 patients receiving continuous probenecid (1 to 2 gm. per day) for from eight months to four years, the average sustained fall in serum urate level was 44% of the premedication level.[195] In moderately or mildly afflicted patients receiving an average dose of 1 gm. a day, if the level of serum uric acid was in the range of 8 to 12 mg.%, the ultimate level averaged 6.8 mg.%; if the initial value ranged from 6 to 8 mg.%, the normal range was subsequently reached.[3054] These objectives might not be obtainable if there was renal damage or extensive tophi; even with daily doses of 2 to 3 gm. of probenecid, it was impossible in 28% to lower the serum urate level below 7 mg.%. A negative urate balance, with disappearance of tophi, however, could be obtained in many cases when the serum urate level remained above 7 mg.%.[1221]

Because of great individual variation in uricosuric response, and in the interest of effective and economical therapy, serum urate levels and average daily ex-

cretion of urinary urate were determined before treatment, and periodically thereafter as a guide to adequate dosage. Commonly, then, 0.5 gm. of probenecid was prescribed for the first week; in each succeeding week an additional tablet was added, until the patient was taking 1 to 2 gm. daily. Since the amount of urate excreted might be as much as twice the usual amount during the first four or five days of probenecid therapy, the early results could not be considered in establishing the proper dose. With the serum uric acid as a guide, the dose of probenecid was increased if the serum level had not fallen to 6 mg.% or less; the dose was rarely to exceed 2 gm. a day.[2978] Recommendations regarding dietary restriction varied from a low-purine, low-fat, restricted protein (60 to 80 gm. a day) diet[1221] to an initial purine-free diet which was liberalized with achievement of significant effect from the drug,[2830] to simple recommendation of a restriction of purine and fat and avoidance of alcohol.[174, 3054]

Once the uricosuric regimen was instituted and maintained, in no instance did new tophi appear in 55 cases of tophaceous gout maintained from six months to seven years on probenecid.[1221] In 36 patients, tophi already formed were much diminished in size or disappeared completely; in 31, the response was unequivocal but only moderate or slight. Impaired function of one or more joints due to chronic gouty arthritis was present in 52 patients; in 37, there was complete resolution of joint disability, and in 12, moderate or considerable improvement.[1221] Relief of joint stiffness and pain in chronic gouty arthritis, healing of ulcerated tophi, restoration to gainful employment and normal or near-normal activity after variable periods of continuous therapy were reported.[195] Decrease in size of bony defects was well documented in serial radiographs.[176, 2978, 3053, 3395]

Uricosuric drugs had no value in treatment of acute gouty arthritis. [This fact is still insufficiently appreciated by the profession at large.—Ed.] Lowering the serum urate level to normal did not relieve the acute attack; indeed, such lowering (in 17 of 55 cases) was associated with precipitation of acute gouty arthritis when probenecid was used.[1221] For these reasons, it was thought best to introduce uricosuric therapy in the intercritical period, after stabilization with prophylactic colchicine.[176, 1221, 2565] Some experienced investigators, however, remained unconvinced that the incidence of attacks of gout increased with initiation of uricosuric therapy.[3057]

Opinions differed on the prophylactic benefit of prolonged probenecid administration to prevent recurrence of acute gouty arthritis; 27 patients who took colchicine and probenecid regularly discontinued probenecid without recurrent acute gout, while nine who discontinued colchicine prophylaxis developed recurrent acute attacks and had to resume daily colchicine, again with good response.[1221] Reduction in the incidence of attacks was attributed to the use of probenecid.[2565, 2881, 2978, 3054]

There was lack of agreement on the knotty problem of the indication for uricosuric agents in nontophaceous gout. There was merit in their use to lower high serum urate levels to normal, but the disadvantages of protracted uricosuric medication had to be weighed against the advantages in the unpredictable clinical course of gout.[1221, 2008, 2565, 2881, 2978] A 66% control with maintenance colchicine left much to be desired when "complete, maintenance control is almost certain" with added dietary restriction, plus daily use of a uricosuric agent. In no instance of nontophaceous gout was a daily dose larger than 1 gm. of probenecid required.[176]

In some cases, failure was due to inadequate dosage (intolerance, renal colic), or immoderation in diet; in some instances, tophi were refractory despite a satisfactory uricosuric response; ". . . evidently some tophaceous deposits are not accessible to humoral agents."[1221] The opinion was expressed,[176, 195, 1221] however, that the most important factor in the effectiveness of the uricosuric agent was the degree of renal function. In the gouty patient with severe renal disease, it was not a lack of responsiveness at the renal tubular level which limited the usefulness of probenecid, but rather the reduction in glomerular filtration rate that limited the possible uricosuric response.[2721] Under these circumstances, uricosuric doses of salicylates might be more effective, but it was hoped ". . . that some new approach [might] be developed to correct hyperuricemia, perhaps by an injectable uric acid metabolizing substance."[1589] [In recent months, an attempt to diminish uric acid production by a compound (6-diazo-5-oxo-L-norleucine, or DON) known to block purine synthesis was partially successful; side-effects, however, limited clinical usefulness of this drug (Grayzel, A. I., Love, E., and Seegmiller, J. E.: Bull. Rheumat. Dis. **10**: 195 [Sept.] 1959).—Ed.]

Despite the great and practical interest in whether prolonged uricosuric therapy would reverse the changes in gouty kidneys, especially in the relatively early stages of the pathologic process, very little new information was forthcoming,[195] although instances were described in which present-day measures ". . . appear to have halted renal progression, at least temporarily," and also very likely delayed the formation of urate calculi.[246, 982]

The risk of precipitating renal colic or the formation of urate calculi with uricosuric drugs was greatest in those patients who had stones or gave a history of repeated renal colic. Frank pain or passage of urate stone or gravel occurred in 15 patients receiving probenecid, 11 of whom had had such difficulties before treatment.[1221] A large fluid intake and sodium bicarbonate or other alkalinizing agents were recommended.[195, 1221] The danger of uric acid stones was not as real as was originally feared;[3057] but prophylactic use of probenecid to prevent renal damage in the hyperuricemic relatives of gouty patients was still impractical.[1676]

Toxic effects of probenecid were minor and infrequent. In seven years, of 160 patients receiving the drug, eight (5%) developed a drug rash and 13 (8%) complained of severe gastric distress; no serious toxic effect upon the bone marrow, liver, etc., was observed.[1221] Sensitization to probenecid occurred in 1 to 2% of individuals;[128] fatal massive liver necrosis as a hypersensitivity manifestation was recorded.[2518] Skin eruptions in children occurred when probenecid was administered concomitantly with penicillin for its renal tubular blocking effect.[380, 3007] Delay of excretion of bromides taken with probenecid was associated with toxicity.[1704]

Uricosuric drugs needed to be continued throughout the life-span[176] or indefinitely,[2978] especially in those severely afflicted; the moderately afflicted could probably revert to small doses after maximal mobilization of urates had been achieved,[174, 2832] and the mildly afflicted person could discontinue probenecid for a period of time after having adhered to the regimen for two or three years.[3047, 3050] "Escape" from the effects of probenecid was very rare; metabolism of probenecid was reviewed;[2830] a reducing substance, thought to be a glucuronic acid conjugate, occurred in patients receiving probenecid, but the urinary excretion of alpha-amino nitrogen was not altered.[195] The effect of probenecid on

serum phosphorus and calcium in hypoparathyroidism, pseudohypoparathyroidism,[822, 1542, 1545] and toxemia of pregnancy was reported.[581, 1375, 1376, 1377]

Whether aspirin nullified the effect of probenecid was disputed.[195, 2565, 2721, 2978] [Most would agree that, on the basis of present information, only occasional doses of salicylates should be used while probenecid is being taken.—Ed.] The addition of probenecid in patients on phenylbutazone or its analogue was associated with decrease in serum urate;[2301, 2881] there was no contraindication to phenylbutazone for the acute gouty arthritis of a patient taking probenecid.[2830]

Salicylates. As long ago as 1877, See observed reduction in size of tophi and increase in urate excretion with salicylates.[1363] Sodium salicylate or aspirin, in a dosage of 90 gr. (6.0 gm.) per day, was about 10% more effective than probenecid;[2008] uricosuric effect of salicylates was potentiated with large doses of sodium bicarbonate,[1221] but there were problems with concomitant salicylate toxicity.[1221, 1704, 2301, 2830] Use of sodium salicylate was especially recommended for marked hyperuricemia (above 10 mg.%).[2008] In two patients with gout and moderately severe renal involvement, 4.8 gm. per day of sodium salicylate orally had a greater suppressive effect on reabsorption of urate than did 1 gm. of probenecid.[2721] Precautionary measures against urate deposition in the urinary tract were the same as for probenecid.[195]

The previously reported antagonistic effect of salicylates on the uricosuric action of probenecid was a variable finding which deserved careful reinvestigation;[195, 2565, 2978, 3380] an action at multiple system sites was suggested for the variability.[1281] Aspirin in varying doses antagonized the effect of thiophenylpyrazolidine and sulphoxyphenylpyrazolidine.[1705, 2301] The addition of caffeine and/or glycine to aspirin enhanced its uricosuric effect.[1705] [This needs to be investigated further.—Ed.]

Phenylbutazone. The rate of synthesis, destruction, or extrarenal disposal of urate was not significantly affected by this drug.[3380] In common with other uricosuric preparations, phenylbutazone possessed a dual action, with urate retention when its blood level was below 10 mg.%.[2830, 2881] Daily doses of 300 to 600 mg. decreased the frequency and severity of acute attacks of gout without consistent reduction in serum urate level; doses in excess of this were not well tolerated,[2881] and the slight uricosuric effect of these doses could be neutralized by retention of water.[2010] The uricosuric action of phenylbutazone ranged from good to excellent, and compared favorably with that of other uricosuric drugs.[2301] [It is generally agreed, however, that the relatively large dose range required for uricosuria of potency, and the potential hazards associated with such doses given for prolonged periods, markedly restrict use of phenylbutazone as a uricosuric agent.—Ed.]

Analogues and Metabolites of Phenylbutazone. Knowledge of uricosuric activity of phenylbutazone stimulated study of the antirheumatic and uricosuric properties of a series of pyrazole derivatives.[448, 1281, 3390] The analogue, 4-(phenylsulfoxethyl)-1-2-diphenyl-3,5-pyrazolinedione (G-25671), which in man possessed anti-inflammatory properties, produced negligible sodium and water retention and was a potent uricosuric agent.[3390, 3393] Thus, by substitution of various groups in the butyl side chain, dissociation of antirheumatic and sodium-retaining properties was achieved. In isolation studies with this preparation, a metabolite identified as the sulfoxide[86] exerted a more pronounced uricosuric effect than did the parent drug; chemically, this was 1,2-diphenyl-4-(2-phenyl-sulfinethyl)-3,5-pyraxolidinedione, better known as G-28315, or sulfinpyrazone. [Now available commercially under the trade name of "Anturan."—Ed.]

These drugs were effective in the ionic form by blocking uric acid reabsorption by the tubules.[448]

The comparative clinical effectiveness of these derivatives was reported.[86, 449, 1704, 1705, 2301, 3395] In 44 gouty subjects under observation for periods of up to 16 months, 400 mg. daily of sulfinpyrazone produced a mean increase of 65% in 24-hour urinary urate excretion, and a mean fall of 30% in serum urate levels; this response was comparable to that obtained with 800 to 1,200 mg. per day of thiophenylpyrazolidine, or 1.5 to 2.0 gm. or more per day of probenecid. Some but not all patients refractory to probenecid in doses of up to 3.0 gm. per day responded to 800 mg. per day of sulfinpyrazone. A favorable effect upon tophi was established, usually after the seventh month of regular use of the drug; precipitation of acute gout occurred upon initiation of therapy, and several patients developed renal colic, with or without hematuria and passage of urate calculi or gravel.[1221, 3395] The availability of different uricosuric agents for special therapeutic problems in tophaceous gout was advantageous;[1221, 3395] there was also some advantage from combining sulfinpyrazone with zoxazolamine. A favorable experience with sulfinpyrazone in the presence of renal abnormality was compared to the previous effect of probenecid.[1705] [These newer preparations, used alone or in conjunction with other uricosuric agents, appear to hold promise of special usefulness.—Ed.]

Gastrointestinal disturbances were the most frequently reported complication of use of phenylbutazone derivatives. Although the drugs were administered with food, milk, and antacids, they aggravated or reactivated peptic ulcers; other side reactions were similar in kind and incidence to those observed with probenecid.[1221] As with all pyrazole derivatives, close medical supervision and periodic blood counts were recommended. Such drugs were to be given cautiously, if at all, to patients with known sensitivity to phenylbutazone and other pyrazoles; one instance of leukopenia possibly related to sulfinpyrazone was described.[3395]

Small doses of salicylates blocked the uricosuric action of either phenylbutazone derivatives, but there was no apparent blocking effect when probenecid, phenylbutazone, or the phenylbutazone derivatives were used in combination with each other.[2301]

Zoxazolamine. A skeletal muscle relaxant, 2-amino-5-chlorobenzoxazole (Flexin) was discovered by fortuitous observation to possess striking uricosuric properties.[449, 2488] The structure of this compound was entirely different from that of other known uricosuric agents; moreover, zoxazolamine was a weak base, whereas phenylbutazone derivatives, cinchophen and salicylates were strongly acidic. After oral administration, a peak plasma level (five- to sixfold increase in C_{urate}/C_{inulin}) appeared between the first and third hours, and disappeared after seven hours. A transitory effect could be elicited with doses as low as 15 mg., since less than 1% was excreted in the urine and virtually complete biotransformation occurred.

The potency of zoxazolamine was of the order of 15 to 50 mg., and was comparable to 30 to 50 mg. of sulfinpyrazone, 100 to 120 mg. of probenecid, 700 mg. of phenylbutazone, and 1,000 mg. of salicylate.[449] It was advised that the drug be administered in divided doses throughout the day. Zoxazolamine, even in doses of 1 gm. per day, produced an unsatisfactory uricosuric response in a patient who also did not respond to probenecid or sulfinpyrazone. [More information on the long-term effects of this preparation is obviously required; loss of effectiveness of this drug over the course of several months has been observed by one of us (I.F.D.)—Ed.] Toxic reactions associated with use of zoxazolamine as a muscle relaxant included gastrointestinal disturbance, drowsiness, lightheadedness, headache and transient skin rashes; except for the latter, these were not

encountered with the relatively low dosages sufficient to elicit a uricosuric response, and at these doses, the muscle relaxant effect was not to be expected.[449] Nephropathy was described.[610] Pyrazinamide and salicylates counteracted the uricosuric action of zoxazolamine, and probenecid and sulfinpyrazone had an additive effect; three and one-half-fold rise in C_{urate}/C_{inulin} produced by 0.25 gm. of zoxazolamine promptly doubled after probenecid was given intravenously.[449]

Anticoagulant Drugs with a Uricosuric Effect. The uricosuric effect of ethyl biscoumacetate [2301] was roughly comparable to that of 1 gm. of phenylbutazone, 6 gm. of aspirin, and 3 gm. of probenecid; dicumarol had a similar effect,[819, 1236] but with maintenance doses the serum urate level rose again to a fairly constant value.

Hyperuricacidemic Agents

Antituberculous Agents. Since the report by Yeager in 1952 of joint pains without objective findings in one fourth of tuberculous patients treated with pyrazinamide, there was increased clinical and investigative interest in this preparation.[704, 759, 1187, 1281, 2709, 2759] Four years later, clinical gout, hyperuricemia and decreased urinary uric acid output were reported [704] in patients receiving 1.5 to 3.0 gm. of this drug per day; [2759] with discontinuation, increased serum urate levels were reduced, although an excess of urate sometimes persisted.[1187] In the intercritical phase of gout, reduction in urinary urate excretion and rise in serum urate were established within two hours; urate clearance reduction, consistently reaching levels to 5 to 10% of control values, due to enhanced tubular reabsorption, was calculated to exceed 99% of the filtered load in most cases; the lowest doses produced an early paradoxic fall in urate clearance.[3390]

Coincidental administration of streptomycin, isoniazid, para-aminosalicylic acid and pyrazinamide did not produce hyperuricemia, although the latter could delay elevation of serum urate. Probenecid caused an initial lowering of elevated levels in a few cases, but continuous use did not prevent the return of pyrazinamide-induced hyperuricemia. In patients receiving sodium salicylate or aspirin, pyrazinamide failed to produce hyperuricemia.[759, 2759] In one patient, ACTH completely reversed the elevated serum uric acid changes.[759]

The relationship between pyrazinamide administration, hyperuricemia, and gout was not entirely clear. Whether all patients on the drug might be expected to develop hyperuricemia was unknown. Precipitation of acute gouty arthritis occurred only after several weeks of therapy; the gouty diathesis was present in half of those who developed an acute attack.[3391] Discomfort might be limited to arthralgia; [1187] renal damage or tophi were not described. [The characteristic features of acute gouty arthritis were not well described.—Ed.]

Chlorothiazide. This substituted benzothiadiazine compound with a free sulfonamide group was a potent, orally effective, nonmercurial diuretic which altered renal ion transport by a mechanism not completely established; significant elevation of serum urate without significant change in renal function was reported in eight individuals receiving 2 gm. daily.[1819] Acute gouty arthritis and hyperuricemia in two patients receiving prolonged chlorothiazide therapy for hypertension were described; [655, 779] in others, unexplained joint pains, especially in the feet, accompanied hyperuricemia. However, some of the highest uric acid levels were not associated with arthralgia.[2324] The effect of 1 gm. of chlorothiazide

daily was studied in two normal individuals and three patients with gout; one of the latter, after six days, developed a rise in serum urate from 4.7 to 12.1 mg.%.[779]

Miscellaneous. Infusion of sodium lactate was associated with striking transitory reduction in urinary uric acid excretion; this was not accompanied by unequivocal rise in serum urate. The fact that no other metabolite shared this effect on urate excretion to such a pronounced degree strengthened the physiologic significance of lactic acid as a regulator of tubular urate reabsorption. High fat diets caused a rise of serum urates, though the rise was less marked.[3391] Decreased uric acid excretion also resulted from large doses of benzoic acid,[3380] ergotamine, atropine, and posterior pituitary solution.[2759] Hyperuricemia and uricosuria also resulted from nitrogen mustards and allied agents, adrenocortical steroids, x-ray, and certain disease processes.

Studies in Colchicine

The mode of action of colchicine in gout remained an enigma; it might be independent of any direct metabolic interference.[3175] In careful metabolic studies, therapeutic doses of colchicine produced retention of sodium chloride and water, and minor increases of sodium and chloride in sweat; adrenal activity was not stimulated.[1871] Administration of colchicine in acute gouty arthritis caused no significant variation in total ketosteroid excretion or in urinary steroid fractionation pattern.[635] Colchicine-induced pruritic vesicular dermatitis in a gouty patient was described.[1464]

In animal experimental studies, one or two doses of colchicine, N-desacetyl-thiocolchicine or N-desacetyl-methyl-colchicine, destroyed litters of rats; subsequent fertility and reproduction were not impaired.[3076] Intra-uterine injection of colchicine in mice before mating induced heteroploidy in many embryos.[887, 888] Greatly increased numbers of mitotic figures observed during the first day after colchicine administration were due to arrest of mitosis at the metaphase, and possibly to stimulation of mitosis.[3060] A linear relationship was established between time and dose of colchicine and the production of mitotic poisoning.[1292] The effect of colchicine on the utilization of labeled thymidine during chromosomal reproduction was described.[1793] In mice given whole-body irradiation, survival was considerably better among those given a colchicine derivative than among the controls; [2875] however, high sensitivity to x-ray was not related to pretreatment with colchicine.[728] Large intragastric doses produced marked necrobiotic mucosal changes, including the occurrence of mitotic figures and various cellular alterations.[2832] Intraperitoneal injection in young rats produced pineal metaphasic arrest which was related to animal age, although it was not influenced by sex hormones.[2444] In rabbits, colchicine administration was associated with antibody production, possibly following upon stimulation of the division of primitive cells from which spring the antibody synthesizing cells.[3060] In the hamster, the effect of colchicine on the nervous system was the main factor causing death.[64, 3135] Colchicine depressed the central nervous system in mice; direct infusion of colchicine into the mammalian nerve produced extensive degeneration by an unknown mechanism.[148] L-ascorbic acid either enhanced or antagonized, depending partly on pH cellular reaction to colchicine.[2202] An improved chromatographic-spectrophotometric method for extraction, separation, and purification of colochicine from plant tissue was described.[2876]

Studies of Cinchophen. A patient with toxic hepatitis and agranulocytosis, possibly due to cinchophen sensitivity and benefited by cortisone, was reported; toxicity was related to *in vivo* liberation of free benzone or nitrophenols.[2967] Sufficiently large doses of cinchopen (3 gm.) had a markedly stimulating effect on urate excretion as well as a depressing effect on plasma uric acid levels in normal human subjects; [686]

[688] this was attributed to depression of tubular reabsorption of uric acid.[688] [Smaller doses are also often effective uricosuric agents.—Ed.] Resistance of the rabbit to gastric ulcers induced by cinchophen and histamine was reconfirmed;[2441] the process of ulcer formation and the genesis of pain in dogs to whom cinchophen was chronically administered were described.[1565] Diminution of duodenal and pyloric mucous secretion by cinchophen was not associated with *in vitro* alteration of the mucosa to produce conjugated glucuronides.[3]

The Uric Acid Problem

Purine Biosynthesis and Metabolism. The sequential addition of atoms to form the condensed ring system of the purines and the complex but pivotal enzymatic reactions involved in synthesis of purines were described.[413, 499, 759, 1187, 2968, 2969, 3376]

The purine ring was synthesized from small molecular units readily available from the metabolic pool and, as summarized in the Tenth Review, glycine, formate, carbon dioxide, and the amide-N of glutamine and aspartic acid served as sources for the carbon and nitrogen atoms of the purine molecule. The identity of these organic substrates contributing nitrogen atoms to the purine molecule was confirmed,[1868, 2913] and another pathway of incorporation of the delta-carbon of glycine into the purine ring was demonstrated by way of the succinate-glycine cycle.[2255]

Formation of Phosphoribosylamine. Ribose-5-phosphate was formed by the oxidative catabolism of glucose-6-phosphate. By further phosphorylation and reaction with glutamine, 5-phosphoribosylamine was formed.[948]

Biosynthesis of Inosinic Acid. Phosphoribosylamine and glycine then reacted to yield glycinamide ribotide. [Energy for this process was supplied by adenosine triphosphate.—Ed.] A one-carbon unit at the oxidation level of formate was then transferred from 5,10-methenyltetrahydrofolic, the biologically active form of folic acid. An additional nitrogen was gained from glutamine, and the ring was closed. Addition of a carbon atom from carbon dioxide and a nitrogen atom from aspartate produced the compound 5-amino-4-imidazolecarboxamide ribotide. A second one-carbon unit was derived from 10-formyltetrahydrofolic acid, and the second ring of the purine molecule closed to form hypoxanthine-ribosephosphate, or inosinic acid.[948]

Isolation and identification of intermedial compounds in the biosynthesis of inosinic acid were studied.[1187, 1954] By fractionation procedures it was possible to separate partially the enzymes (Fractions I and II) responsible for one of the steps in the *de novo* synthesis of inosinic acid by pigeon liver extracts, the conversion of 5-amino-imidazole-ribotide to 5-amino-4-imidazole carboxamide ribotide. Neither fraction alone could bring about the conversion; when Fraction I was incubated with the substrates required for the over-all reaction, an intermediate [presently thought to be 5-amino-4-imidazole-N-succinylocarboxamide ribotide.—Ed.] accumulated. Azaserine (which possessed antibiotic and mouse antitumor properties) was a potent inhibitor of inosinic acid biosynthesis *in vitro*, and resulted in an increased accumulation of these ribotides.[1360]

Biosynthesis of Uric Acid. Inosinic acid was a key compound in the interconversion of nucleotides and their conversion to uric acid (figure 1). The nucleotides, adenylic acid, xanthylic acid, and guanylic acid, could be derived from inosinic acid by known reactions. Inosinic acid could also be degraded to the nucleoside, inosine, and then to the free purine, hypoxanthine. Xanthine oxidase converted hypoxathine to xanthine and to uric acid. The other nucleotides could also be degraded to their respective nucleosides and free purines. Guanine, and possibly adenine as well, could be transformed into xanthine. The only established reaction generating uric acid was the oxidation of xanthine by xanthine oxidase.[413, 2255, 2529]

Nucleic Acids. *Structure and Degradation.* Nucleic acids had polynucleotide structure, being composed of nucleotides linked by phosphodiester linkages from the

5′ positions of one sugar to the 3′ position of the next. The composition of the polynucleotides could be determined in part by the composition of the mixture of mononucleotides from which they were formed.[2968] "To make guanine nucleotides from hypoxanthine, adenosine triphosphate is required; to make adenine nucleotides from the same precursor, guanosine triphosphate is required. Because of this curious cross-linkage of 'feedback,' if, for any reason, production of guanylic acid is limited, a limitation in adenylic acid production would be anticipated to ensue and vice versa. Likewise, an over-production of guanylic acid might be expected to result in an increase in rate of generation of adenylic acid and vice versa. Thus, at a chemical level, there exists a novel kind of homeostasis, wherein not the abundance of a substance but rather the ratio of abundance of the pair of products, tends to remain constant."

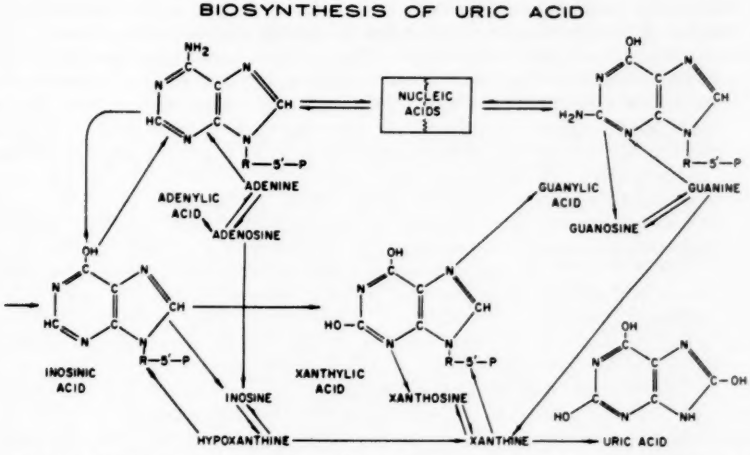

FIG. 1. Inosinic acid (hypoxanthine ribotide), a key compound in the formation of uric acid, had several fates. Conversion to uric acid is shown to occur without the obligatory intervention of nucleic acid.—Wyngaarden.[3376]

Further studies by Stetten showed that nucleic acids were degraded by enzymatic hydrolysis, and that the component nucleotides were split by specific nucleotide-5-phosphatases to yield the corresponding nucleoside and orthophosphate. The nucleoside was then split by nucleoside phosphorylase to yield the free purine base (adenine, guanine, hypoxanthine, or xanthine) and ribose-1-phosphate; adenine, as such, was probably not formed in quantity. The purine bases, as noted previously, could be utilized again in the synthesis of the nucleosides or nucleotides, or could be further degraded to uric acid.

Identification, separation, and biosynthesis of free purine bases not of dietary origin and normally occurring in human urine were described.[280, 3270, 3271, 3272, 3273] The ranges of daily excretion of these compounds (which include hypoxanthine, xanthine, 7-methyl-guanine, adenine, guanine, 1-methyl-guanine, N^2-methyl-guanine, 1-methyl-hypoxanthine, 6-succino-amino-purine and 8-hydroxy-7-methyl-guanine) were determined.[3376] These substances could represent useless methylation by-products, or components of as yet unknown coenzymes or nucleic acids of specialized but unappreciated function. In acute gouty arthritis and in leukemia and polycythemia vera, twofold increases in excretion of 8-hydroxy-7-methyl-guanine had been observed, the first recognized metabolic abnormality of purines in acute gout.[3270, 3271] In asymp-

tomatic gout and in leukemia and polycythemia, significantly decreased excretion of xanthine and hypoxanthine was observed.

The only non-uric acid purine bases thus far detected in plasma were xanthine and hypoxanthine.[3376] The twenty- to thirtyfold increase in hypoxanthine concentration which occurred in blood upon standing was interpreted as being due to breakdown of adenine nucleotides.[544, 1602] Methods for the quantitative separation of xanthine, hypoxanthine and uric acid in plasma [236, 237, 774, 775] and in spinal fluid of normal living subjects and after death were described.[2433] Among all methylated uric acids formed after administration of methylated xanthines to animals, only the 1-methyl derivative was produced by the direct action of xanthine oxidase;[235, 237] a major intermediate, 8-hydroxyadenine, was demonstrated in this reaction.[3375]

Thus, mechanisms were identified by which simple material was incorporated into the purine molecule and eventually into cellular nucleic acid. Mechanisms of degradation of nucleic acid were identified by which nucleotides, nucleosides and, eventually, free purine bases were formed. These purine bases could be utilized again in nucleoside synthesis, or degraded by known pathways to uric acid. This mechanism accounted for the major portion of uric acid produced in the normal and gouty human.

"Shunt Mechanisms." *The Direct De Novo Synthesis of Uric Acid.* The possibility that uric acid might be formed by alternative direct pathways was not excluded by the above studies. In fact, there was increasing evidence in normal and gouty subjects to suggest a more direct pathway (or "shunt mechanism") by which glycine could be converted to uric acid without the intervention of nucleic acids. The rate of incorporation of isotope into uric acid was studied with a number of labeled precursors.[1279, 2721, 3175, 3376] In the majority of gouty subjects having essentially normal basal urinary uric acid excretion, the rate and magnitude of glycine-N^{15} incorporation were indistinguishable from normal.[356] ". . . In certain gouty subjects glycine appears to find its way into uric acid by a rapid route which appeared to circumvent the metabolically sluggish intermediates, particularly the purines adenine and guanine, which are known to be relatively inert metabolically, and particularly in the desoxyribonucleic acids of the adult cell. It was suggested that there might be operative a mechanism, dissimilar to the mechanism normally operative in the bird and reptile. In these species uric acid is known to be the major excretory form of metabolic nitrogen. The bird makes an abundance of uric acid from a variety of nitrogenous precursors and excretes them. However, it is endowed with a kidney capable of excreting urine—which is generally solid or semisolid. We are inclined to picture the gouty individual as having at least a vestige of avian metabolic pathways without being simultaneously endowed with avian kidneys." [2721]

A correlation was shown between the magnitude of urinary uric acid excretion and the rate and extent of glycine incorporation into uric acid. Comment on the inability to demonstrate consistent over-incorporation was: "It has not been made clear whether this inhomogeneity . . . is attributable to quantitative or qualitative differences, i.e., whether the dissimilar patterns of glycine incorporation into uric acid reflect varying degrees of a common metabolic aberration or are the result of different errors of metabolism affecting the alternative pathways"; alternative pathways of glycine utilization were also implicated.[1279] Two alternative interpretations of the findings in gouty "hyperexcretors" were (1) that a disproportionately large fraction of glycine nitrogen was utilized for positions 1, 3 and 9 of the purine ring, or (2) that glycine contributed its nitrogen to position 7 of the purine ring not only by direct incorporation of the glycine molecule *in toto,* but also by other as yet undetermined pathways.[3376]

There were two biosynthetic pathways producing urate in normal man, and the defect in some patients with gout might involve the more rapid and direct of these. In man, 4-(5)-amino-5-(4)-imidazolecarboxyamid (AIC) was incorporated into uric

acid via two pathways—one rapid and direct, the other slower and indirect, presumably via nucleic acids.[2721] In gouty subjects, A1C was incorporated into urinary uric acid in a greater-than-normal amount, and interfered with *de novo* synthesis of uric acid from glycine. In man, hypoxanthine-8-C^{14} was converted promptly and almost directly to uric acid.[3376] Adenine-8-C^{14}, on the other hand, was converted to uric acid by a slower and less direct pathway. In normal, gouty, and leukemic subjects, isotopes rapidly appeared in most of the precursor purines. Since urinary hypoxanthine, adenine and guanine were derived not as free bases but from cleavage of their respective nucleotides, it was likely that, in rapid urate synthesis, cleavage of a portion of the newly formed nucleotide occurred, with subsequent conversion of the free base to uric acid. Inosinic and guanylic acids, in particular, were likely to participate in such shunt pathways. These studies suggested that all subjects produced some uric acid by rapid pathways, e.g., nucleotide cleavage reactions, as well as a larger fraction by slower pathways involving nucleic acid.[3378] It was proposed that, in primary gout, faulty regulation of rates of nucleotide synthesis might exist.[3375] [Thus, substantial evidence supports the concept that overproduction of uric acid is the cause of the hyperuricemia of primary gout, at least in patients with abnormally high urinary uric acid excretion.—Ed.]

Failure of glycine incorporation technics to demonstrate overproduction of uric acid in all cases did not eliminate the possibility that overproduction might be a consistent defect, since uricolysis and/or greater-than-normal dilution of the isotope in enlarged metabolic pools of substrates, intermediate compounds, or uric acid would tend to decrease incorporation values.[3377]

Uric Acid Metabolism in Man. Uric acid was the end-product of purine metabolism in man. The enzyme uricase, which in lower animals further degrades uric acid to allantoin, did not exist in man. Furthermore, man excreted only small amounts of urinary allantoin (5 to 35 mg. daily), generally considered to be of dietary origin. Despite these considerations, there was evidence that uricolysis did occur.[2721, 3376] In the normal male the "miscible pool" of uric acid was about 1 gm., 50 to 75% of which was replaced daily by newly synthesized uric acid. It was calculated that the quantity of uric acid entering the pool daily exceeded the quantity excreted in the urine by 100 to 250 mg. If it is assumed that uric acid was not accumulating, this excess represented uric acid being disposed of by other routes. After intravenous administration of uric acid-N^{15}, significant concentration of isotope was found in urinary urea and ammonia as well as uric acid, demonstrating uricolysis.[3376] That this was not the result of uricolysis by intestinal bacterial flora was shown when essentially the same results were obtained by repetition of the experiment after effective intestinal bacteriostasis. The organic site where uricolysis occurred was not yet identified.

Leukocytes and erythrocytes—but not serum—of normal individuals had the capacity to degrade uric acid, probably by virtue of the verdoperoxidase content of white blood cells, and cytochrome oxidase and peroxidase activity in red blood cells.[257, 3175] The average destruction of urate observed with blood cells from gouty patients was slightly less than that with cells from normal subjects; diminished uricolysis could account for the accumulation of uric acid in some gouty persons. In humans, a significant percentage of uric acid-2-C^{12} was oxidized to $C^{14}O_2$, indicating that uric acid was not entirely an end product of purine metabolism.[2418] It was further shown that, in some patients with hyperuricemia, a greater-than-normal percentage of uric acid was oxidized.

A highly purified uricase preparation from pork liver mitochondria had enzymatic activity related to the presence of copper, which provided a means of attachment of the substrate onto the enzyme.[197, 198, 1975] A purified uricase from beef kidney was described;[1927] administration of this preparation to chickens temporarily decreased serum uric acid levels, and in two humans, one of whom had tophaceous gout, pro-

duced a definite reduction in serum acid levels, with accompanying increase in urinary allantoin.[1926] The uric acid and uricase-resistant residue in plasma in patients with renal insufficiency [1259] and in normal man [2201] was studied.

The unique uricogenic effect of 2-substituted thiadiazoles in man was reported.[1762] Oral administration of 2-ethylamino-1,3,4-thiadiazole hydrochloride (an agent with antitumor effect) to eight adult patients with advanced cancer was associated with marked increase in serum uric acid levels, which promptly returned to normal when the drug was discontinued. In five of the eight, urinary uric acid rose, paralleling the increase in serum uric acid and indicating that a renal mechanism was not involved.

Metabolic Studies Associated with Hyperuricemia and "Secondary Gout." [Previous Rheumatism Reviews included reports of glycine-N^{15} incorporation into uric acid in secondary gout in a patient with secondary polycythemia, and in a patient with myeloid metaplasia.—Ed.] More extensive studies on the biosynthesis of uric acid from glycine-N^{15} in primary and secondary polycythemia,[3392] in myeloid metaplasia (without gout) with glycine-1-C^{14}, and in chronic myelogenous leukemia with AIC-C^{14},[3376] have been reported. The results and interpretations were generally similar; the predominant route of uric acid formation seemed to be through nucleic acid biosynthesis and subsequent degradation. [The importance of these involved studies is considerable. They demonstrate that the predominant pathways of uric acid biosynthesis are different in secondary and primary gout, in spite of their similarities in clinical manifestations and therapeutic responses.—Ed.]

Metabolic studies of the defect in essential hyperuricemia as the sole and earliest recognizable manifestation of primary gout were limited to investigation of renal regulation of urate excretion; the data, for the most part, were within limits of normal variation.[982, 3392] On the basis of the rate and cumulative curves of glycine-N^{15} incorporation into uric acid, it was not possible to determine whether clinically overt gout had developed or would develop.

Uric Acid Metabolism in Animals. The excretion of urea, ammonia, uric acid, and allantoin by newborn babies, pigs, and puppies was studied and the results were compared with values for adults of the same species.[3299] In studies of age changes in protein excretion in the whole life cycle of the male rat, the normally excreted quantities of protein increased sharply with age; the excretion of both uric acid and nonprotein nitrogen increased in middle age when growth ceased; a second rise in the excretion of these constituents occurred as the rat approached death.[939] X-irradiation of fasting rats caused an increased excretion of uric acid (75 to 206%) and allantoin (39 to 74%) during the first 24 hours; the increase in total purine excretion was the result of tissue breakdown, with concomitant loss of nucleic acids and other purine-containing compounds.[1539]

Inhibition of uric acid biosynthesis in birds (chickens, pigeons, and cormorants) was demonstrated by intravenous infusion of o-diazoacetyl-L-serine (azaserine) and 6-diazo-5-oxo-L-norleucine (DON); this was prompt, and was demonstrated by a parallel fall in plasma and urine uric acid due to a block in purine biosynthesis. "The steps leading to the synthesis of uric acid in the intact pigeon and in the *in vitro* pigeon liver system appeared to be identical up to the formation of inosinic acid. In the *in vitro* pigeon liver system, the end point of purine biosynthesis was inosinic acid, since the pigeon liver lacks xanthine oxidase necessary for the oxidation of inosinic acid and, finally, hypoxanthine to uric acid. In the intact pigeon, however, xanthine oxidase was found to be present in other organs, mainly the kidneys, and the process is carried to the end point, uric acid, before excretion. Chickens differed from pigeons in that their livers contain xanthine oxidase. It was, therefore, of interest that azaserine and DON, which inhibit purine biosynthesis *in vitro* by acting as glutamine antagonists and blocking the conversion of formyl glycineamine ribotide to the next product, were demonstrated to inhibit the *in vivo* production of uric acid in the intact pigeon, chicken and cormorant." The inhibition of uric acid synthesis in birds by

azaserine was reversible; uric acid production recovered in chickens within 24 hours.[1763]

Convulsions and death occurred within a few days in chicks fed a diet containing 45.6% galactose; the blood galactose and uric acid were markedly elevated; the kidneys showed cellular degeneration in the glomeruli and tubules, and a precipitate was seen in some of the tubules but not further identified. One of the enzymes involved in the transformation of galactose to glucose was probably a factor limiting the ability of chicks to metabolize large quantities of this sugar.[2912]

Microörganisms (four pseudomonad isolates) existing in litter droppings could utilize uric acid aerobically as their sole carbon, nitrogen, and energy source. Organisms harvested from media containing uric acid could degrade it completely with the formation of carbon dioxide and ammonia; allantoin, allantoid, glyoxylic and formic acids were completely oxidized.[134]

Reduction and release of ferritin iron during anaerobic incubation of ferritin with rat liver slices were due to an accumulation of uric acid in the tissue and its diffusion into the medium, together with marked sensitivity of uricase to low oxygen tensions.[1239, 1240]

Physicochemical Properties of Uric Acid. The possibility that uric acid might exist in forms other than as simple molecules in true solution was further investigated. Uric acid was present in plasma only as the free ion.[1603] Studies with zone electrophoresis of serum and synovial fluid from patients with gout, nephritis, and leukemia showed that uric acid consistently migrated as a single band, with mobility about 15% greater than that of serum albumin; only insignificant amounts of uric acid could be recovered from other sections of the paper.[2652, 3175] Systemic or intra-articular administration of prednisone, phenylbutazone, probenecid, or pyrazinamide did not alter the electrophoretic behavior of uric acids. On the other hand, it was re-affirmed that uric acid exists in serum in both a protein-free fraction and a fraction bound to albumin; the affinity of uric acid for albumin differed in normal and pathologic sera.[2201] Since uric acid could be separated from albumin by dialysis, the binding was physical rather than chemical.

The ratio between concentration of urate in blood corpuscles and in plasma in 10 subjects ranged from 0.46 to 0.75, with an average of 0.55; although little was known of the state of uric acid within the blood cells, it was possible that it might exist there entirely or in part as riboside or ribotide from which uric acid was released enzymatically.[1603] The diffusion coefficient of urate for a human connective tissue membrane (cerebellar tentorium) was determined; no correlation was observed between the coefficient values obtained and the age of the individual from whom the tissue was obtained.[1838]

The "Collagen Disease"

General Concepts. There was a tendency to replace the term "collagen disease" by "connective tissue disorders," since collagen was but one component of connective tissue and since, moreover, the other components played an equal or greater role in the pathogenesis of these disorders.[435, 2479, 2903] Several excellent reviews of the structure of normal connective tissue appeared.[63, 893, 1675, 2896, 3316, 3422] The ground substances were important in the pathogenesis of collagen diseases.[331]

The nature and origin of fibrinosis, a histologic finding common to all collagen diseases, were re-investigated with newer technics.[2214] Although through fluorescence microscopy, fibrin was demonstrated to be a component common to fibrinoid from various diseases, fibrin of blood thrombus differed from fibrinoid in its histochemical properties.[2222, 3355] Fluorescence microscopy showed the presence of

fibrin where conventional methods gave negative results.[680, 1148, 2215] Evidence was presented indicating that the main constituent of fibrinoid might be a derivative of smooth muscle.[2222] In systemic lupus, fibrinoid resulted from degradation of the desoxyribonucleic acid (DNA) component of the nucleoprotein in mesenchymal cell chromatin;[1740] "fibrinoids" from various diseases had differing susceptibilities to proteolysis.[3194] These findings suggested that "fibrinoid" encompassed a heterogeneous group of materials.

The role of hypersensitivity and allergy in the pathogenesis of these diseases was reviewed.[136, 460, 685, 718, 767, 1931, 2085, 2229, 2523, 3404] Although there was a similarity between the cardiac, pulmonary, and vascular lesions of collagen diseases and those which occurred in protracted anaphylactic reactions in man and animals, it was emphasized that identity of lesions was not proof of identity of etiology.[319,2523] Total body irradiation of rabbits 24 to 72 hours before sensitization with horse serum brought about a marked reduction in the number and intensity of vascular lesions and of carditis;[685] this was considered to indicate that such lesions depended upon antibody production and immune mechanisms. Gamma globulin was demonstrated by means of the fluorescent antibody technic at the site of the lesion of acute rheumatic carditis, in rheumatoid nodules, in the splenic and renal lesions of systemic lupus, and in the L.E. cell inclusion body.[3167, 3168] The same technic showed that sera of patients with systemic lupus, scleroderma, and dermatomyositis contained a factor which bound with intranuclear material of homologous and heterologous tissues.[160] These observations were consistent with, but not proof of, the presence of an antigen-antibody reaction in the tissue lesions. That serum complement levels were low in active systemic lupus might be explained by fixation of complement *in vivo* by an antigen-antibody reaction.[3318] However, elevation of serum complement occurred in R.A., acute rheumatic fever, active dermatomyositis, and periarteritis nodosa.

The possibility that pleuropneumonia-like organisms might be the common denominator in the etiology of all collagen diseases was again discussed.[418] [The possibility of infectious origin, including filtrable viruses, deserves more than the scant attention it is receiving.—Ed.]

It was again stressed that personality structure and function played a significant role in secondary reactions to the collagen diseases; psychiatric conditions might be of etiologic importance.[399]

A phenylene-diamine derivative was capable, in rats, of reproducing the histopathology of all of the more common connective tissue diseases.[1122] [This interesting and important work requires confirmation and expansion.—Ed.] 2,5 dihydroxyphenylpyruvic acid (2,5-DHPPA), an intermediary metabolite of phenylalanine and tyrosine, was detected consistently in the urine of patients with collagen diseases; administration of L-tyrosine aggravated the clinical condition of the patients.[2280] A block of intermediary metabolism of phenylalanine and tyrosine at the metabolic stage from 2,5-DHPPA to homogentisic acid was suspected of being one of the most important etiologic factors in collagen diseases. [This work awaits confirmation.—Ed.] That 24-hour urinary excretion of glucuronides was significantly lower than normal in various rheumatic diseases awaited satisfactory explanation.[1472]

General manifestations of the collagen diseases were described and the multiplicity of symptoms and signs was again stressed.[102, 629, 647, 1286, 2140, 2142, 2457, 2528, 3055, 3056, 3134] Ocular manifestations of collagen diseases were noted, scleral in-

volvement being frequent.[230, 631, 2036] Pulmonary manifestations were reviewed.[906, 1384, 2246, 2388, 2479] Radiologically, it was difficult to determine which changes were due to the primary disease *per se*, and which to complicating edema and infections.[2388] Histologically, apart from vascular involvement, the alveolar walls themselves showed areas of fibrinoid necrosis and hypercellularity. A severe proliferation of alveolar lining cells and organization of fibrin exudate produced a microscopic appearance of "carnified lung." Irregular cystic changes occurred (especially in scleroderma) as a result of the organization of the fibrinous exudate.[1789] Color reactions of skin sections stained with a combination of alcian blue and periodic acid Schiff showed tinctorial similarity between disseminated lupus and dermatomyositis, but none among the other collagen diseases.[522]

Two patients with a systemic disease characterized by marked chronic eosinophilia, visceral involvement, and hypergammaglobûlinemia were described; the term "disseminated eosinophilic collagen disease" was proposed.[916] Two cases of symmetric, recurrent fat necrosis were described as "collagen diseases."[39] [This contention was not well supported.—Ed.] Five of 12 patients with congenital agammaglobulinemia or hypogammaglobulinemia developed chronic arthritis, and one child had dermatomyositis.[1560] The question was raised of the relationship of multiple antibiotic injections to the appearance of this case of dermatomyositis.

The "rheumatoid factor" was found in a variety of collagen diseases, although most frequently in the serum of patients with rheumatoid arthritis.[926, 3419] Rheumatoid factor was found in 48% of cases of systemic lupus erythermatosus (S.L.E.), 33% of polyarteritis nodosa, and 26% of scleroderma.[1421] Increased anticomplement, antistreptolysin, and sensitized sheep cell agglutination titers were common in R.A., S.L.E., polyarteritis nodosa, various types of myositis, cirrhosis, and "purpura hyperglobulinemia." These observations were related to the hypergammaglobulinemia which occurred in these diseases. The changes in serum proteins, glycoproteins, and mucoproteins in rheumatic diseases gave no more useful information than did other "acute phase reactants."[2567] However, distinct patterns could be distinguished by chromatographic separation of serum mucoids.[2438] No difference was noted in excretion of hydroxyproline between normal adults and patients with collagen diseases.[3414]

The general treatment of collagen diseases was discussed;[242, 335, 1354, 1402, 1791, 1861, 2060, 2977, 3183] the dangers of indiscriminate corticosteroid therapy were discussed. That hormonal therapy neither cured the disease nor arrested its natural progression was reiterated.[194, 335, 434] [The therapeutic value of corticosteroids appears to be more definite in S.L.E. than in other members of the "collagen disease" group. Some reliable clinicians consider that, in some cases, long-term corticosteroid therapy may favorably influence the course of lupus. Most consider that it may be life-saving during acute exacerbations.—Ed.]

Systemic Lupus Erythematosus (S.L.E.)

Clinical Features. Many reviews emphasized the historic as well as the clinical and pathologic aspects of this disease.[78, 104, 359, 439, 644, 826, 902, 1214, 1368, 1431, 1968, 1967, 2042, 2303, 2475, 2753, 2797, 3101] There was great concern over the apparently rising incidence of systemic lupus. A Swedish follow-up study of hospitalized patients with S.L.E. indicated little change in incidence between 1938–39 and 1948–49, but a sharp increase between 1948–49 and 1954–55.[3019] [This change

was undoubtedly due, in part, to a difference in the criteria used for the diagnosis of S.L.E. in the two periods.—Ed.] There were four reports of more than one case in the same family,[1150, 1246, 1860, 3192] including one instance in identical twins.[3292] [One of us (D. C. G.) has seen S.L.E. in an adult brother and sister, the diagnosis being firmly established in both cases.—Ed.] S.L.E. also occurred in a North American Indian.[1761]

The effect of pregnancy on S.L.E. was discussed.[1866, 2232, 2233, 3138] Progressive albuminuria in the mother was an ominous sign, which might warrant termination of the pregnancy, though the opposite conclusion was also arrived at.[1060] Exacerbation of the disease after delivery was described.[3009] Onset of S.L.E. during pregnancy was misdiagnosed as toxemia of pregnancy in one patient.[357] Fetal mortality was apparently increased by S.L.E., while live babies were unaffected.[1060, 2232, 2233] Two reports agreed that S.L.E. in children differed from that in adults only by its lesser predilection for the female.[866, 3410]

Skin Manifestations. Discoid lupus and S.L.E. were regarded as the same disease process.[45, 486, 824, 826, 1785, 1999, 2496] In addition to clinical and laboratory evidence of such a relationship, there was a histopathologic similarity of the skin lesions.[45, 1785, 2496] An important study was carried on in 35 patients, all thought previously by dermatologists and internists to have uncomplicated cutaneous forms of L.E. without any systemic manifestations.[1785] Seventeen subsequently had low grade fever; 10, arthralgia; eight, pulmonary fibrosis or pleural disease; six, Raynaud's phenomenon; seven, hepatomegaly or splenomegaly; nine, anemia, and 20, leukopenia (white blood cell count less than 5,000). The sedimentation rate was elevated in all but three patients.

The occasional association of subcutaneous nodules with discoid lupus was described as "lupus erythematosus profundus."[108, 1033, 1272, 2318, 3189] These nodules occasionally antedated other skin lesions, and responded favorably to bismuth, gold, or antimalarial treatment.

Articular Manifestations. The articular symptoms were often more notable than the physical signs.[2816] Articular manifestations ranged from arthralgia to chronic deforming arthritis with flexion contractures and x-ray evidence of destruction of cartilage.[157, 2140, 2181, 2816, 3364] Occasionally there was a migratory arthritis which resembled that of rheumatic fever.[2112, 2140, 2816] A case of simultaneous bilateral rupture of the ligamentum patellae was recorded.[2001]

Renal Manifestations. The natural history of lupus nephritis was studied with the aid of serial renal biopsies.[2219, 2413] The earliest lesion, a glomerulitis, was often accompanied by protein, leukocytes, and/or leukocyte casts in the urine; occasionally the urine was normal, and in such cases, renal involvement could be diagnosed only by renal biopsy. As the renal lesion progressed, erythrocytes and granular casts usually appeared in the urine, while epithelial cellular casts, fatty casts, and oval fat bodies appeared occasionally. Subsequently, renal function decreased and azotemia increased. If death did not intervene, most patients with progressive lupus nephritis passed through a nephrotic stage. Occasionally, the nephrotic syndrome was the initial manifestation of the disease. A "pseudonephrotic" syndrome, characterized by edema, hypoproteinemia, proteinuria, and normal serum cholesterol levels, had a particularly grave prognosis.[2413] Although occasionally acute and fulminating, lupus nephritis more commonly ran a fatal course of from one to four years.

Pulmonary Manifestations. Pulmonary manifestations received additional emphasis and were studied in 54 autopsied cases.[2170] Pulmonary manifestations of S.L.E. could be conspicuous at any stage; pleuritis, with or without effusion, was a common early feature.[906, 1642, 3343] The x-ray appearances were usually nonspecific, and difficult if not impossible to distinguish from those of superimposed infection.[651, 1211, 1920, 2170] Pathologic alterations of a specific sort, such as fibrinoid necrosis of arterial walls, were demonstrated in only a minority of cases.[29, 907]

Neuropsychiatric Manifestations. Neuropsychiatric symptoms and signs were reported in 24% of 100,[565] in 35% of 40,[2298] and in 65% of 55 patients.[1970] Convulsions, hemiplegias, and visual or auditory disturbances predominated. Psychotic episodes occurred in 17% to 52% of patients at varying times, sometimes antedating other manifestations of S.L.E. by some years.[398, 490, 564, 565, 2514]

Gastrointestinal. Gastrointestinal symptoms and signs in 87 patients were considered to be "minor" in 25 and "major" in seven; of the latter, five had an adynamic ileus and two had chronic ulcerative colitis.[406] Several instances of acute and severe abdominal symptoms were observed;[2414] of 14 such patients, four had pancreatitis (fatal in three). S.L.E. and chronic ulcerative colitis exhibited many interesting similarities.[405] Four of eight patients with both an active chronic hepatitis and ulcerative colitis also had typical L.E. cells and were considered to have systemic lupus.[1233] Other patients were described who had active, chronic hepatitis as the dominant clinical feature of lupus;[179, 1968, 3041] some termed this condition "lupoid hepatitis."[1968] Conversely, postnecrotic cirrhosis was sometimes mistakenly diagnosed as lupus.[1330]

Other Manifestations. Several cases of peripheral gangrene occurred, but this was an atypical manifestation.[1646, 1968] The association of "auto-immune" hemolytic anemia and of "idiopathic" thrombocytopenic purpura with S.L.E. was again emphasized.[719, 1251, 1818] In three instances, splenectomy for "idiopathic" thrombocytopenic purpura was followed by overt manifestations of S.L.E.[719] It was postulated that the spleen had had some controlling effect on the disease.

Pathology. The general microscopic pathology was reviewed.[2837, 3069] Fibrinoid formation in S.L.E. represented degradation of nucleic acid;[1740] the fibrinoid of glomerular wire loops and the splenic arteriolar onion-skin lesion represented an abnormal mucoprotein secreted by mesenchymal cells.[3069] However, in skin the Feulgen stain for desoxyribonucleic acid (DNA) gave negative results, both in fibrinoid material and in vessel walls.[2439] There was an increased content of ribonucleic acid (RNA) in fibroblasts and monocytes, increase in periodic acid Schiff (PAS) positivity in or about collagen bundles, and fibrillation or destruction of the basement membranes.

The renal lesions were studied by both light and electron microscopy.[915, 937, 951, 2218, 2219] Serial renal biopsy showed the earliest changes to be those of a focal glomerulitis, with progression into a subacute glomerulonephritis with epithelial crescents.[937, 2218, 2219] Alternatively, the lesion began as an irregular basement membrane thickening, which progressed later to wire-loop lesions, and finally to the picture of subacute or chronic glomerulonephritis. In an excellent paper, the electron microscopic appearances of the kidney in lupus nephrosis and in glomerulonephritis were described.[951] They could be distinguished from each other in early lesions; at later stages the changes were not always characteristic.

In early S.L.E. there was a generalized basement membrane thickening with a variable degree of endothelial proliferation; fibrinoid material was seen between the basement membrane and the endothelium; epithelial changes were late.

Histologic and histochemical studies of lymph nodes were reported;[290, 697, 2191] the early change was a cellular proliferation, especially of plasma cells. Vascular lesions were prominent in pathologic studies of three patients with systemic lupus, two of whom also had features of scleroderma;[2761] these lesions represented occlusion of lumina by fibrin or protein coagula, which in time were converted into intimal thickenings. Synovial biopsies did not permit differentiation between the synovitis of systemic lupus and that of rheumatoid arthritis.[2144, 3411] [Further progress in synovial biochemistry might be more rewarding than histologic studies to date.—Ed.]

A vacuolar change in muscle fibers was discovered in a single case, and was considered perhaps to be specific (despite its admitted uniqueness).[2368] [Such a conclusion on the basis of a single case report hardly seems warranted.—Ed.]

Laboratory Findings. *The L.E. Phenomenon.* The clinical significance and specificity of the L.E. phenomenon were widely discussed.[421, 536, 621, 667, 1025, 1062, 1063, 1210, 1398, 1428, 1713, 1858, 1943, 2243, 2304, 2343, 2355, 2613, 2792, 2802, 3307] Some observers claimed that L.E. cells were found in some patients with discoid lupus[421] but not in others.[1431, 1943, 2304] The incidence of positive L.E. cell preparations in R.A. varied from none[1431] to 64%;[2343] significance was uncertain.[185, 2802] Other conditions in which L.E. cells were found included penicillin and tetanus antitoxin serum sensitivities, the hydralazine syndrome, phenylbutazone sensitivity, postnecrotic cirrhosis, and tuberculosis.[621, 667, 1062, 1063, 1398, 1428, 2343, 2792, 3307]

The underlying mechanism of the L.E. cell phenomenon was intensively investigated. In vivo transfusion of L.E. serum caused positive L.E. cell preparations in the recipient's blood.[216] One of the serum factors responsible for the L.E. phenomenon was a gamma globulin.[491, 946, 1470, 3324] Isolated leukocyte nuclei sensitized with this gamma globulin were phagocytosed by functional leukocytes to form the classic L.E. cell. Pictures were published of phase-contrast and interference microscopy of lymphocyte nuclei acted upon by L.E. serum to form L.E. bodies, with subsequent ingestion of the latter by living leukocytes.[2535] Complement appeared to be necessary for phagocytosis of the L.E. body. Thus, some negative L.E. cell tests in patients with classic S.L.E. might have been due to lack of active complement.[1025] Cytochemical studies showed that, in the formation from a nucleus of the L.E. cell inclusion body or hematoxylin body, histone was either degraded and lost, or else masked by an abnormal protein.[1164, 1165, 1166, 1167, 1168, 1169] In addition, there was some loss of DNA. [This is a revision of the original interpretation that the L.E. cell inclusion body was simply depolymerized DNA.—Ed.] A one-molar sodium chloride extract of nuclei (presumably containing nucleoprotein, among other things) was acted upon by L.E. serum to form L.E. bodies, which were then ingested by living white cells to form L.E. cells.[1469] Nucleoprotein could be substituted for whole nuclei in the formation of the L.E. cell inclusion body.[1427]

Methods for demonstrating the presence of the L.E. serum factor represented a major recent advance. There were a number of reviews of existing technics,[627, 823, 1367, 2302, 2798] and some modifications[311, 732, 947, 1117, 1411, 1712, 2240, 3423] for demonstrating the L.E. cell phenomenon. Most modifications depended upon traumatizing the leukocytes in some way so that they might be more easily acted upon by the L.E. factor.[1117, 2240] It was pointed out that nucleophagocytosis with

formation of "tart cells" needed to be carefully distinguished from the true L.E. cell.[1215, 1396] [This is most important, since nucleophagocytosis is commonly reported, falsely, as the L. E. phenomenon.—Ed.] Phagocytosis of cryoglobulin crystals was another source of confusion.[1397]

The presence of L.E. factor was demonstrated by fluorescence microscopy. It could react with nuclei of both human and animal origin.[74, 1455, 1470] Reproducible titers were obtained by exposing calf thymus nucleohistone spots on glass surfaces to serum dilutions and then staining the spots with fluorescein-labeled or radioiodine-labeled antihuman gamma globulin.[1072, 1073, 1074, 1075, 1076, 1077] There were reports of positive complement fixation tests employing lupus serum and either DNA or whole nuclei.[528, 2366, 2547] A hemagglutination test was described, using tannic acid-treated sheep red cells coated with DNA.[1980, 2136] A neucleoprotein-latex agglutination system was also described, and was found to be a practical tool for measuring lupus factor.[550]

Other Findings. Clinical laboratory abnormalities in S.L.E. were reviewed.[1332, 1850] A simple test, performed by adding para-toluene sulfonic acid to undiluted serum and observing precipitate formation, was believed to be useful in S.L.E.[1591] However, further evaluation showed that this test was nonspecific and depended upon the presence in serum of raised gamma globulin levels.[354, 898, 3305]

Leukocyte agglutinins were found in nine of 12 cases.[1716] However, L.E. serum had the property of inhibiting the leukocyte agglutinating ability of normal serum, and the leukocyte agglutination inhibiting factor was identical with the L.E. factor.[1849]

Several cases with a circulating anticoagulant were described.[340, 480, 1834, 2466, 3031] The anticoagulant was a gamma globulin which, in some cases, was an antithromboplastin, and in others seemed to interfere with the formation of prothrombin or thromboplastin.[3031] The biologic false-positive test for syphilis was studied in 148 persons, of whom 42% were subsequently diagnosed as having "collagen disease" and 7% as verified S.L.E.[2186, 2187, 2188] Others reported similar experiences.[1759, 2157, 2513]

The levels of "acute phase reactants," in both blood and urine, were found to be raised.[13, 332, 772, 1312] [The examination of acute phase reactants rarely gives more information than does the sedimentation rate. See Section on Rheumatic Fever.—Ed.] The electrophoretic distribution of serum glycoproteins was found by some to permit differentiation between idiopathic thrombocytopenia and that due to S.L.E.,[1972] even though serum protein electrophoretic changes in S.L.E. were nonspecific.[155, 962, 1325, 2311] Electrophoretic changes consisted of decreased albumin, with a rise in the alpha and gamma globulin components; "active cases" tended to have low beta globulins and a tendency to increased fibrinogen.[155] A decreased affinity of serum for Congo red in S.L.E. as well as in rheumatoid arthritis and other diseases depended partly upon elevation of serum glycoprotein.[1823] Studies of blood pantothenic acid (a precursor of coenzyme "A") showed a diminished ratio of boundover free pantothenic acid in patients with S.L.E.[2845] [This needs to be confirmed.—Ed.]

Etiology and Pathogenesis. The presence of gamma globulin at the sites of renal lesions was demonstrated by fluorescence microscopy.[2107, 2108, 3042] The existence of an antigen, if any, remained hypothetic. A popular theory was that the body loses tolerance to its own nucleoprotein or some other cellular constituent. Both leukocyte agglutination and nucleophagocytosis could be induced by antisera to white cells or their constituents.[2137] Antisera to cytoplasm and mitochondria were most effective in provoking leukocyte agglutination, whereas antisera to nuclei and nucleoprotein caused nucleophagocytosis. [This important work requires confirmation and expansion.—Ed.] The possibility of an auto-im-

mune reaction against many of the body's own tissues was stressed by a group which demonstrated complement fixation by L.E. sera using extracts of various organs as antigen.[1093, 1966]

An allergic etiology was speculated; the role of drug allergy was explored. A syndrome resembling S.L.E. following therapy with hydralazine for hypertension was again reported.[929] One observer claimed to have produced experimental S.L.E., with L.E. cell-formation and wire-loop renal lesions, in dogs to which hydralazine had been administered.[620] [Other similar studies are considered in the Section on Experimental Arthritis.—Ed.] However, other workers could not duplicate these findings.[874, 1103] Two patients were described in whom the administration of sulfonamides might have either provoked or exacerbated S.L.E.[238, 1477] The administration of Mesantoin to two epileptic patients was thought to be the cause of ensuing lupus.[1903] It was postulated that the high incidence of epilepsy as an early symptom of S.L.E. could be due to analeptic drugs themselves.

A patient with chronic discoid lupus was described in whom injections of neither an autogenous vaccine of hemolytic streptococci nor an antiserum to hemolytic streptococci had provoked the systemic disease, although the antiserum did cause an increased erythema of the skin lesions.[1230] This experience would seem to provide some evidence against the theory of streptococcal sensitivity.

Placental transmission of the L.E. factor was described.[240, 473, 2139, 2241, 2328] The factor disappeared after a few weeks, and the infants remained healthy. A neonatal death, where the mother had acute S.L.E., was ascribed to a combination of congenital S.L.E. and endocardial fibroelastosis.[1454] [The evidence for S.L.E. in the infant was scant.—Ed.]

Nine patients with various disorders who had received large doses of somatotrophic hormone developed thickening of the glomerular basement membrane in the kidney similar to that seen in S.L.E.; a possible etiologic relationship was considered.[2585] [Clinicians should be alerted to any possible etiologic factors in various patients and report them, however unlikely they may seem. Such reports could prove more helpful than repetition of the time-worn descriptions of clinical manifestations of S.L.E.—Ed.]

Hematoxophil bodies in the tissues might be derived from L.E. cells lodged in the capillaries, because this appearance could be produced experimentally.[1118]

Treatment. Corticosteroids were still the mainstay of therapy, but the initial extreme enthusiasm for these drugs was waning.[825, 827, 829, 830, 1348, 1430, 1626, 2894, 3413] [This can be attributed at least partly to an unwarranted overenthusiasm initially, rather than to decreased interest in the effectiveness of these preparations. —Ed.] Some urged that steroids be reserved for the treatment of the acute crisis of S.L.E.[2548] [The impression held by some that the course of this disease may be favorably modified by long-term continuous corticosteroid therapy is not yet well supported.—Ed.] Antimalarials were most helpful when used in combination with steroids;[223, 552, 2047] often they allowed the dosage of steroids to be lowered.[3416]

Polyarteritis Nodosa (P.A.N.)

Clinical and Pathologic. Clinical differentiation between "polyarteritis nodosa" (P.A.N.) and "allergic vasculitis" was stressed.[2049] Fever, weight loss, asthma, neuritis, leukocytosis and renal disease were more often found in poly-

arteritis nodosa than in "allergic vasculitis," in which purpura and urticaria were more common. Complete recovery "never" occurred with P.A.N, as it did with "allergic vasculitis." [We find it difficult to subdivide arteritis on a clinical basis. —Ed.] Several retrospective reviews of case material of polyarteritis were presented.[135, 2594, 2595, 2818] The sex ratio was 3:1 in favor of males.[2818] The number of cases diagnosed, particularly among the elderly, was increasing.[2595]

Cutaneous manifestations occurred in 25% of the cases. They were often due to blood vessel involvement, and were manifested by purpura, gangrene, nodules, livedo reticularis, and ulceration.[1901, 2034, 2133, 2618, 2630, 2655] The location of the affected vessels frequently necessitated deep subcutaneous biopsy.[1901]

Pulmonary involvement in 32 of 111 patients was associated with features which were rare or completely absent in groups without pulmonary involvement: the disease affected the sexes equally; the incidence increased with age; the main clinical features were those of asthma, pneumonia or chronic bronchitis; the interval before lesions were evident in other organs might be months or years, especially in patients with asthma; a high eosinophilia was prominent; and necropsy showed severe lung damage, including nodules or tissue lesions, hemorrhagic phenomena, cavities, infarcts, fibrosis, and bronchiectasis.[2592, 2595]

Hypertension was less frequent and alimentary tract involvement more frequent than in the group without lung involvement. Three cases of pulmonary hypertension due to P.A.N. confined to the pulmonary vessels were described.[2925] Hemoptysis, multiple lung infarcts and cavitation,[2673, 2891, 3403] and difficulties of interpreting chest x-ray findings were discussed.[1479, 2682] Lung biopsies in five patients with similar bilateral pulmonary infiltration with small nodular densities radiographically showed, in all cases, angiitis and granuloma formation in which epithelioid cells and eosinophils were prominent. Only one of these patients had extrapulmonary lesions, and all had a benign clinical course. The relationship of this condition to Wegener's granuloma (see this section below) was discussed.[1479]

Gastrointestinal involvement was found in 70% of 111 patients,[2595] and several individual case reports appeared.[582, 1753, 2075, 2440, 2873, 3090] P.A.N. caused or simulated appendicitis, appendiceal abscess, gastric ulcer (even radiologically), and intestinal obstruction. It caused death from intraperitoneal hemorrhage in one patient, and death after six episodes of jejunal perforation in another. Three cases of polyarteritis involving only the stomach and small bowel were recorded.[1846]

Involvement of the nervous system was the subject of several case reports. One patient had a peripheral neuropathy, together with spinal cord involvement;[1250] his lymph nodes contained abundant cells staining with pyronine blue, and this was postulated as evidence of a hyperimmunizing process. This patient died of cerebral hemorrhage, as did another who, in addition to peripheral neuropathy, had had cord transection on a vascular basis.[1295] P.A.N. was misdiagnosed for two years as multiple sclerosis in one man.[1064] A patient with mononeuritis multiplex was described.[1721]

Cardiac lesions were found in nine of 12 patients, eight of whom had congestive heart failure.[135] Coronary artery involvement was most common, but a pancarditis also occurred. A case of endomyocardial sclerosis associated with polyarteritis in a child of 12 years was described.[3240] Among the vascular mani-

festations of P.A.N., Raynaud's phenomenon progressing (but only rarely) to gangrene of all fingers was described.[1243] [In our experience, this is not a rare manifestation of polyarteritis nodosa.—Ed.] Also described were patients having venous as well as capillary and arterial involvement.[1719, 1752]

Renal involvement by the arteritis was common. In one case simulating chronic glomerulonephritis, autopsy revealed P.A.N.[1489] Another patient had hydronephrosis due to ureteral involvement.[3200] R.A. associated with P.A.N. was described and the relationship between the two diseases discussed.[996] The possibility of precipitating polyarteritis nodosa by corticosteroid therapy for rheumatoid arthritis was emphasized. [Multifocal areas of arteritis may occur in severe systemic rheumatoid disease, with or without corticosteroid therapy. It has not been established that these lesions are identical with those of the disease "polyarteritis nodosa."—Ed.] Hypertrophic osteoarthropathy due to polyarteritis, but without associated lung lesions, was noted.[1945] In another patient, periostitis in the absence of joint involvement was attributed to polyarteritis.[2679]

The ocular changes in polyarteritis nodosa were reviewed and a case of albuminuric retinitis was reported.[313] Autopsy demonstrated involvement of posterior choroidal arteries and also of the choriocapillaris, but the retinal vessels themselves were free; this was considered to support the view that albuminuric retinitis in P.A.N. was due to cardiac and renal involvement and not to local disease. However, a case was described of acute polyarteritis nodosa of retinal vessels.[2773] The association of Cogan's disease (interstitial keratitis and vestibulo-auditory symptoms) with P.A.N. was again suggested,[358, 683] and two patients with autopsy evidence of coincident P.A.N. were reported.[683] There was continued controversy as to whether Wegener's granulomatosis was a variant of P.A.N. or a distinct entity; the characteristic features of intractable granulomatous rhinitis and sinusitis, pulmonary nodules, and a terminal fulminating uremia were described.[949, 967, 1203, 1410, 1643, 1853, 1873, 1902, 2579, 2790, 2828, 2852, 2925, 2988, 3000, 3078, 3132] Clinically, there were marked constitutional features and a rapidly fatal course (a few months).[3217] Pathologically, granulomata (often with giant cells) were found in the nose, paranasal sinuses, upper respiratory tract, lungs, spleen, and other organs; there was also usually a severe glomerulonephritis. Eye lesions were found in 19 of 44 patients.[3000] Multiple granulomata were also found in the liver.[547] However, most patients showed pathologic evidence of a widespread arteritis.[949, 1203, 1853, 1873, 2076, 2579, 2988, 3217, 3218] [Thus, while undoubtedly the clinical course of these patients places them in a separate group, pathologically they do not show such clearly defined differences from patients with P.A.N.—Ed.]

Laboratory Findings. Marked eosinophilia (greater than 1500/cu.mm.) was thought to be limited to patients with lung involvement.[2593] Coexisting acute porphyria hepatica and P.A.N. was presented.[2225] It was suggested that porphyrinuria might be more frequently discovered in P.A.N. if it were sought.[2225]

Etiology and Pathogenesis. Two cases of P.A.N. had abundant plasma cells in and around the lesions.[2197] In another case, fluorescence microscopy revealed gamma globulins localized in the acute vascular lesions of P.A.N., whether occurring in the arteries or in the glomerular capillary tufts.[2106] These findings supported a hypersensitivity theory of etiology. The hypothesis of hypersensitivity to drugs, and particularly to sulfonamides, was discussed.[135, 1582] Circulating antibodies to penicillin were demonstrated in one patient both by passive serum transfer and by passive cell transfer.[2087] [Unfortunately, a control experi-

ment, using normal serum and normal cells, was not made; furthermore, the patient's illness started with acute tonsillitis, and an infectious etiology was not excluded.—Ed.] Among 366 routine cholecystectomies, there were 55 cases (15%) of "allergic cholecystitis" with local vascular changes of P.A.N.[1900] Involvement of the gallbladder was also noted in other cases.[135, 582] It was suggested that the gallbladder might be a target organ for P.A.N.

In a series of 111 patients, there was a high incidence of drug administration (particularly of sulfonamides) prior to the onset of P.A.N. However, etiologic significance could no more be attached to the drug than to the conditions for which it was given; hypersensitivity to bacteria, particularly to the hemolytic streptococci, was suggested.[1901, 2593, 2594] Further evidence of an infectious etiology was suggested by the report of P.A.N. in a patient with sarcosporidiosis[2059] and in a patient with tuberculosis.[1061] [However, the evidence for P.A.N. in the latter case is inadequate.—Ed.]

Evidence was again presented that renal arterial ligation in the rat was followed within a few days by the development of widespread lesions resembling those of P.A.N.[1751] It was shown also that, in the unilaterally nephrectomized monkey, overdosage with a potent mineralo-corticoid could produce P.A.N., among other things.[2740] Prolonged administration of follicle-stimulating hormone to rats led to the production of P.A.N. which was secondary to a mineralo-corticoid-producing pituitary tumor induced by the follicle-stimulating hormone.[2382] Polyarteritis nodosa thus experimentally produced could not be attributed to hypersensitivity. The theory that hypertension is a predisposing factor in the development of periarteritis in rabbits was disproved.[2041]

Treatment. A report of the effects of cortisone after one year was inconclusive because the untreated group (control) had a lesser incidence of hypertension than did the treated group.[82, 2099] Another report of the effects of corticoids contained no control group of patients.[1582] While cortisone often produced quick relief of symptoms and signs, its long-term effectiveness was not so clear-cut.[82, 2099, 2791] The dangers of corticoid therapy were reiterated.[41] [But P.A.N. is inherently a fatal disease, with its own "dangers."—Ed.] Sympathectomy was reportedly beneficial in a patient with "midline granuloma."[110] Local x-ray therapy to the lesions of Wegener's granulomatosis was advocated.[3217]

Dermatomyositis

Clinical. The incidence was 2:1 in favor of females.[276, 553] Association with malignancy[987, 1599, 2716] occurred in 6.7% of 270 patients,[553] and in as many as 43% of 14 patients,[2771,2772] but not in children.[553, 938, 2771]

An association with idiopathic Cushing's syndrome was noted in two cases.[553] In one patient, dermatomyositis was not unfavorably affected by pregnancy.[1155]

The rash varied, and was most common about the eyes and forehead.[2086] The symmetry of skin lesions was striking in one patient.[2294] Extensive skin involvement was associated with a worse prognosis than polymyositis alone.[2012] In some instances, the skin almost escaped involvement.[1327] Calcinosis was found most often in the younger age group.[553] Gastrointestinal manifestations were common, including hemorrhage and perforation. Dysphagia occurred in 60% of 270 patients.[553] Six of 19 adolescents and children had radiologically demonstrable involvement of the hypopharyngeal muscles; this was of prognostic im-

portance, as five of the six died.[938] Other manifestations included interstitial pneumonitis,[2160, 2294] congestive heart failure,[469, 2653] pericarditis,[460] and pulmonary hypertension.[469]

Pathology. The muscle changes[938, 1845, 2160] revealed that edema was the first change, followed by loss of transverse striation, granular degeneration, and often marked vacuolation. Proliferation of the muscle fiber nuclei was regularly seen. In the interstitial tissue, edema was the essential change, at times accompanied by an infiltration of histiocytes and lymphocytes. The wide diversity of lesions, both from patient to patient and within a single section, was emphasized. The changes could be distinguished from those found in scleroderma, polyarteritis nodosa, and systemic lupus. Only one paper emphasized fibrinoid necrosis as a feature of dermatomyositis.[2086] These authors also found vasculitis of medium-sized vessels.

Laboratory Findings. Mild anemia and elevated sedimentation rate were found.[2086] L.E. cells in the peripheral blood were reported.[553, 1509, 2653] The electrocardiograms of *27* patients were studied;[3199] 30% had abnormal tracings, most commonly the nonspecific finding of low-amplitude QRS complexes in the standard leads. In *22* of the *27* patients, these findings were thought to signify an altered pattern due to abnormal cutaneous electrical resistance, rather than to myocardial disease. The electromyogram of four patients showed polyphasic motor units, short fibrillation-like potentials under voluntary control, and a myotonia-like response.[2301] These findings were thought to be characteristic.

In the acute phase, urinary creatine excretion was increased and creatinine excretion decreased.[555] Remission was accompanied by a reversal of this finding. However, these were extremely variable findings in dermatomyositis, and of dubious value in either diagnosis or prognosis. While the serum transaminase levels correlated well with the activity of the disease, it was also emphasized that this finding had no diagnostic significance.[2196] [A positive test for the "R.A." factor may be present.—Ed.]

Etiology. The possible etiologic relationship to penicillin and other drug administration was discussed.[938, 1509]

Treatment. Advantages and disadvantages of corticoids were again reviewed.[152, 938, 2012, 2059, 2131] Nitrogen mustard seemed to help one patient,[2012] but the disease in some patients was self-limiting without treatment.[2086] Because of a possible streptococcal origin, prolonged antibiotic treatment, as in rheumatic fever, was recommended to prevent recrudescence.[2086] [This remains unproved. —Ed.]

Scleroderma

Clinical. There was confusion as to whether scleroderma was a single disease entity; a variety of descriptive terminology was used, such as "sclerodactylia," "scleroderma," "acrosclerosis," "acroscleroderma," "progressive systemic sclerosis," "morphea," "guttata morphea," and "linear scleroderma."[710, 3338] The distinction between scleroderma and acrosclerosis occurring with systemic sclerosis was reiterated. An occasional association of scleroderma with malignancy appeared.[554, 616, 1024, 1517, 1598, 2525, 2933, 2934, 3343] In the skin, calcinosis often occurred, and was detected radiologically prior to the development of clinically obvious calcium deposits.[554] Associated Raynaud's phenomenon was noted in a small group of patients,[554, 832] and it was reiterated that Raynaud's phenomenon

appeared some years before other symptoms.[554, 2003] The importance of renal involvement in scleroderma was noted by several authors.[474, 1040, 1322, 2016, 2017, 2021, 2577] Pericardial effusion,[2109] congestive heart failure,[3337] and myocarditis [1517] were also described. The electrocardiogram was abnormal in from 10% to 75% of patients;[930, 2933, 3337, 3338] patients with clinical evidence of visceral involvement had the highest incidence of abnormal electrocardiographic signs.[930] Multiple cysts were found in the lungs of a patient with scleroderma who eventually died from a tension-hemothorax.[1526]

The previous literature concerning scleroderma of the gastrointestinal tract was thoroughly reviewed.[1177] Every area, from the esophagus to the colon, had been reported as involved. The symptoms were often those of regional enteritis or idiopathic ulcerative colitis.[99, 256, 1178, 1998, 2610] The appearance of the small bowel at operation when involved by scleroderma was described.[1998] Scleroderma associated with hepatic fibrosis and portal hypertension was reported in two patients.[473] A case of cord compression due to dural involvement by scleroderma [1629] and two patients with atypical trigeminal neuralgia were noted.[2742] Sclerodermatous involvement of the cornea,[672] muscles of mastication,[546] and periodontal tissues [1207, 2853] was described. Scleroderma was associated with widespread osteopoikilosis in one case.[3275] Pregnancy had no effect on scleroderma, or vice versa.[3107]

Pathology. In the skin, epidermal changes were nonspecific, but changes in the cutis were of some importance.[2310] The fundamental changes were edema, homogenization, fibrosis, and sclerosis of the collagen fibers, and a varying degree of sclerosis and obliterative changes in the vessels of the cutis. There was thickening of the cutis in generalized scleroderma, but thinning in morphea and acrosclerosis. The muscles involved in scleroderma showed dense interstitial cellular infiltrates, with increase in interstitial collagen.[1845] Muscle fiber degeneration, if it occurred, was secondary to the invasion of the interstitial spaces. The heart muscles showed similar changes.[3251] The lungs contained much fibrous tissue, in which there were many cystic spaces lined by a columnar ciliated epithelium.[1526] Lipoid-filled macrophages were found in the alveoli. In the small bowel, there was marked infiltration by collagen which replaced the muscular layer.[1998] Gangrene of a large segment of colon was due to extensive fibrosis affecting arteries in the bowel wall.[1982] The renal changes were similar to those seen in malignant hypertension, and consisted of intimal thickening of the small interlobular arteries and arterioles, fibrinoid necrosis of afferent arterioles and glomerular loops, and focal cortical infarction.[583, 995, 2577] Synovial biopsy in three instances showed evidence of acute or chronic inflammation.[2576]

Laboratory Findings. L.E. cells were found in a patient with scleroderma.[107] Renal clearance of calcium and phosphorus was normal in one patient with calcinosis.[1078] Although glomerular filtration rates in 25 patients as measured by creatinine clearance were normal, the renal plasma flow as measured by para-aminohippuric acid clearance was reduced in 80%.[3146] Serum protein studies on 45 cases showed an increase in gamma globulin which was proportional to the degree of total involvement.[2934] The cutaneous abnormality was reflected by an abnormally high uptake of radioactive sulfur by the involved skin,[755] and a decreased rate of disappearance from the skin of blebs produced by intradermal injection of normal saline.[2765] Other findings suggested that sweat glands were functionally normal despite their abnormal histologic appearance.[2381]

Etiology. In three patients, abnormal tryptophan metabolism was found, and the pattern of urinary metabolites resembled that found in nonscleroderma-tous individuals after the administration of antimetabolites of pyridoxine.[2435] These biochemical abnormalities were reversed after treatment with either pyridoxine or ethylenediaminetetracetic acid (EDTA). These results favored the concept that, in scleroderma, the abnormal metabolism resulted from a functional deficiency in tissue magnesium. Gold miners on the Witwatersrand had an unusually high incidence of scleroderma; half of the cases had radiologic changes in the lungs due to scleroderma, and distinguishable from those of silicosis.[927] Sclerodermatous skin changes in a patient with a functioning carcinoid suggested that serotonin might be a factor in the pathogenesis of scleroderma.[3401]

Scleroderma was a primary disease of "collagen and ground substance," while acrosclerosis was secondary to vascular disease.[1515] This view was supported by the finding that sensory chronaxy was prolonged in both involved and clinically uninvolved skin in scleroderma, but only in involved areas in the acrosclerosis associated with Raynaud's phenomenon.[1531]

Treatment. Prednisone was administered to six patients for short periods (up to four and one-half months); some benefit was claimed, especially for those with skin tightening and joint pain.[2576] [More adequate study of long-term steroid therapy in this disease is urgently needed, but preliminary results today with steroids for scleroderma are not encouraging.—Ed.] Rapid progression of the renal lesion and possible deleterious effects of corticoids and hypotensive agents upon the renal disease were discussed.[608, 2577] EDTA had favorable effects in three patients.[2631] [This treatment must be regarded as still in the investigative stage, and used only when it can be appropriately controlled by experienced observers. At least one death attributable to the drug has been recorded.[575]—Ed.]

The hormone relaxin was used in 23 patients, and relieved vasospasm and promoted healing of trophic ulcers;[512] some relief of skin tightness was also described.[512, 1522] Ultrasound to the hands and the paravertebral cervical regions (aimed at the cervical sympathetic chain) was beneficial in two patients.[3130] Intravenous procaine administered to 71 patients delayed progression of the disease.[952] Parathyroidectomy was followed by a "cure" in a case of generalized scleroderma.[710]

Psoriatic Arthritis

Arthritis associated with psoriasis was of several types. That resembling rheumatoid arthritis was different from so-called psoriatic arthropathy, which was more destructive and affected asymmetric distal interphalangeal joints.[497, 955, 2607, 3372, 3373] All but two of 34 patients studied had a negative modified sensitized sheep cell agglutination test; of the two with a positive test, one was the only patient with tendon sheath effusions and subcutaneous nodules. "Erosive arthritis" was not the same as R.A.[3372, 3373]

The clinical picture varied so that it was difficult to separate the patients into two or three groups, especially when accompanying spondylitis was considered.[2607] Major features of "erosive arthritis" associated with psoriasis as contrasted with uncomplicated R.A. were that (1) it tended to be milder than R.A., though a severe crippling form occurred; (2) distribution of affected joints was much the same, though a predilection for distal interphalangeal joints closely related to affected nails was seen, and (3) there was a high incidence of sacro-iliac involve-

ment. More men than women were affected, and nail changes had occurred in 87% at one time or another. Arthritis tended to parallel nail changes rather than skin involvement, but when the skin was extensively involved the arthritis tended to be severe. None had pustular psoriasis, and no patients with the gross crippling form of psoriatic arthropathy were presented.[3372, 3373] Palms and soles were seldom affected, but joints of the hands and feet were invariably involved, and in over a third of 66 patients (34 males and 32 females) the distal interphalangeal joints of the fingers were affected. Proximal limb joints were also affected in two thirds of the patients. Limitation of movement of the spine was a complaint in three fourths of the patients. In four the spine was rigid. However, the sacro-iliac joints were often normal on x-ray examination. Very few presented the typical picture of ankylosing spondylitis. The differential agglutination test was positive in 28% of the 39 patients tested.[2762] It was suggested that acrodermatitis continua, pustular bacterid, and pustular psoriasis were variants of a single condition. Two of three patients with generalized pustular psoriasis had arthritis.[1516]

Biopsy of synovia of a patient with "rheumatoid-like' arthritis, with affected distal interphalangeal joints, showed changes considered to be characteristic of R.A.[2607] Radiographic changes included marginal erosions at the edges of articular surfaces, most frequently those of distal interphalangeal joints. Bases of phalanges were often expanded and tips sometimes eroded; eventually, they became shortened and pointed.[3374] Tests dependent upon the presence of the rheumatoid factor were usually negative.[2762, 3373] [Recent reports have been more definite in this regard.—Ed.]

A hereditary predisposition to psoriasis was proposed. Among 239 consecutive, nonselected psoriatic cases, 43 (17.9%) were familial. Males as well as females transmitted the disease. Among the index cases, 17.7% had arthritis. The genotype representation was heterogeneous. In a number of cases the predisposition to psoriasis seemed to be caused by a dominant mutant gene which, in its homozygous state, apparently determined the generalized, severe form of the dermatosis.[118] Studies of psoriatic scales pointed to a viral etiology.[2103]

Corticosteroid therapy was palliative in severe exfoliative psoriasis, and arthritic symptoms were often greatly benefited. Severe relapses were uncommon, but steroids were not curative.[973] Rest, physical therapy, and chrysotherapy, in addition to corticosteroids and salicylates, were recommended for the arthritis.[2607]

Reiter's Syndrome

Several reviews and reports were published. The triad of urethritis, conjunctivitis, and arthritis, with the tendency to relapse and recur, and the relatively good prognosis as regards permanent disability, were characteristic.[1018, 1107, 1946, 2037, 2181, 2700] The eponym "Fiessinger-Leroy-Reiter's syndrome" was suggested.[2037] [This hardly seems reasonable, as Sir Benjamin Brodie's writings on this subject appeared almost 100 years before those of any of the three mentioned in this hyphenated eponym.—Ed.] A report appeared of three cases in females, aged 41, 34 and 55.[2492] [These case reports are not very convincing, and hardly fulfill the diagnostic criteria most of us use, but Reiter's syndrome does occasionally occur in women.—Ed.] Reiter's syndrome in first cousins, men aged 36 and 37, was reported.[2207]

No new information concerning etiology or pathogenesis appeared. Failure to demonstrate a viral etiology in nongonococcal urethritis by means of HeLa cell cutures was reported. Urethral washings from 24 cases of nongonococcal urethritis and synovial exudate from two patients with Reiter's syndrome were also investigated in Chang conjunctival and amnion cell cultures for the production of viral cytopathogenic effects. No evidence supporting a viral etiology was obtained.[1018]

Chronic inflammatory changes of the prostate or seminal vesicle were again stressed as important etiologic factors in acute rheumatic states, but only three cases of Reiter's syndrome were included in 190 males.[794] Severe or recurrent cystitis or a persistent vaginal discharge was the genitourinary component in the female.[2931] All patients with nonspecific urethritis associated with an arthritis were included in Reiter's syndrome.[2235] [Confusion in diagnostic criteria has been difficult to resolve to date.—Ed.]

Conjunctivitis was the most common ocular manifestation, but relapsing iritis was reported in up to 25% of patients with arthritis associated with "venereal urethritis." Uveitis was never the initial manifestation, and was anterior in all instances. Eight of 16 patients classified as having Reiter's syndrome had uveitis, and all eight had x-ray changes in the sacro-iliac joints or in the spine or feet.[2931] [Three of the eight were women. This high incidence of sacro-iliac involvement raises the question of diagnostic criteria. No doubt some cases of "venereal urethritis" would be classified by many as ankylosing spondylitis following a urethritis, rather than as Reiter's syndrome.—Ed.]

Sacro-iliac disease demonstrable by x-ray was quite frequent.[2293, 3085] A "seldom recognized" form of Reiter's syndrome consisted of iritis, sacro-iliac arthritis and genital infection; the last two were often asymptomatic or unrecognized. Of 73 patients with Reiter's syndrome, 36 (49.3%) had x-ray changes in the sacro-iliac joints much like those of ankylosing spondylitis; lesions were irregularly distributed, but commonly seen in the lower portion of the joint. Loss of the sharp cortical line, blurred appearance of the joint, erosions, sclerosis, and fusion were seen. In almost 70% of those affected, both joints were involved. Calcification of the paraspinal ligaments was found in only one of the 73. A third of those patients with x-ray changes in the sacro-iliac joints had episodes of anterior uveitis which were often recurrent, while only 8% of those with normal sacro-iliac joints had uveitis.[2293] Other radiologic changes included osteoporosis, erosions of joint margins, periosteal new bone formation, spur formation, destructive lesions of carpal and wrist joints, and sclerosis and irregularity of the symphysis pubis.[2235] Edema of the achilles tendon or patellar tendon, and periosteal new bone formation adjacent to a metatarsophalangeal joint, were frequent.[2517]

Painless mucous membrane lesions of the corona of the glans and/or encircling the urinary meatus were found quite often. Similar lesions in the mouth and on the palate were less frequent. These lesions were so typical that the diagnosis in doubtful cases was sometimes established by their presence.[2181] Lesions on the tongue preceded other manifestations of Reiter's syndrome in one reported case. A biopsy of this superficial tongue erosion showed irregular thickening of the epithelium, with necrosis of the surface. The corium was edematous and contained degenerated collagen fibers, with infiltrations of lymphocytes and plasma cells.[7]

Hyperkeratotic skin lesions or keratodermia blennorrhagica were of diagnostic value and practically specific for Reiter's syndrome.[2181] [We do not agree. —Ed.] Culture of lesions of one of two cases yielded coagulase-positive *S. aureus*.[479] [Cultures from skin lesions frequently yield the staphylococcus. There is no evidence that these are of etiologic importance.—Ed.] Recurrences were common.[1946] Skin lesions usually followed the typical triad, but urethritis was frequently mild and overlooked.

Three cases with pericardial involvement and typical electrocardiographic findings were reported.[700] Biopsy of the synovia of three patients showed mild reduplication of the synovial lining cells and subsynovial edema; inflammatory cellular infiltration was not marked.[3411] Electrophoretic serum protein estimations in 30 patients showed hypoalbuminemia and elevated alpha globulin. Beta and gamma globulins were less markedly or consistently elevated. The degree of change showed a positive correlation with severity rather than duration of illness.[699]

The duration of illness in 70 treated patients was no shorter than in five untreated patients. There was no evidence that any form of therapy influenced the course of the disease.[1029] Although most patients recovered completely from one or several attacks, an occasional patient had residual joint damage and chronic arthritic changes, usually affecting the feet.[1019] ACTH and cortisone in adequate doses for a long enough period suppressed symptoms, even though the course was not shortened. Intra-articular hydrocortisone was of value. No complications of systemic or local treatment were observed.[1032]

Neurotrophic Arthropathy: Charcot's Joints

Although Charcot's joints and painless neuropathic ulcers of the lower extremities were generally attributed to tabes dorsalis and to syringomyelia, diabetes mellitus was a more common cause.[1547, 2091] Similar articular lesions could be encountered in leprosy, peripheral nerve injuries and pyogenic soft-tissue infections following puncture wounds, and other infections secondary to trauma,[328] after injuries of the spinal cord.[1707] Other causes included paraplegia[1908] or spina bifida with impairment of sensibility.[496]

Charcot's joints were the sequelae of physiologic weight forces or repeated trauma on a joint without proprioception. In normal individuals, vectorial weight forces in the lower extremity passed through the body of the astragalus to the ground and were opposed by equal counterforces. Destruction of the astragalar head or of the subastragaloid joint allowed the weight force to pass through the center of the body of the astragalus, with the effect of converting the astragalus into an amorphous mass of condensed bone. The eccentric direction of the weight force resulted sooner or later in fractures of the astragalus and body of the scaphoid bone. Unchecked, this process destroyed the subastragaloid and midtarsal joints; the ankle joint was then secondarily involved.[446]

Spontaneous fractures occurred as occasional complications of Charcot's joints when mechanical demands exceeded the strength of bones.[446, 2920] Posterior apophysis of the heel bone and the ilium were usual sites of these fractures, although other sites included metatarsals, ribs, spinous processes of cervical vertebrae, and bones of the forearm. Weight-bearing joints having free motions were

more often affected by arthropathy than were fixed joints such as sacro-iliac and the superior tibiofibular joints.[446, 447]

Neuropathy in diabetes mellitus was estimated from zero to 66%,[1200] and was almost always associated with an infective element.[1543] Distinctive features of diabetic neuropathy included pains, cramps, numbness, tingling, burning, stinging and needling sensations, characteristically worse at night, and aggravated by exposure to cold. Anesthesia was uncommon. Vibratory sense was lost early; reflexes were reduced or absent.[1200]

Syphilitic arthropathy with destruction proceeded with exceptional rapidity, with absorption of a femoral head in less than five months. Associated massive edema was attributed to rupture of the joint capsule, with liberation of a large quantity of synovial fluid into the soft tissue.[1726] Neuropathic joints in syringomyelia occurred in 20% of patients,[2958] but no instance of arthropathy occurred in another series of 26 cases.[2279] Arthropathic changes in syringomyelia could appear with great rapidity. Absorption of major parts of the right shoulder was complete in less than 10 weeks.[2117] Arthropathies were most often found in the upper extremities.[3182]

Early roentgenograms in diabetic neuroarthropathy showed fragmentation of the articular cartilage and adjoining bone. Small islets of fuzzy bone were seen growing in the synovial membrane.[1547] Synovial punch biopsies made possible more frequent study of articular tissues, and were often informative and of diagnostic aid. Biopsy of a Charcot's joint in a 65 year old woman showed numerous characteristic foci of lime salt deposition throughout the synovial tissues.[2145] [These have also been seen in osteoarthritic synovialis in elderly patients.—Ed.]

Treatment was aimed at prevention of further damage and preservation of weight-bearing function.[3059] Surgical therapy was aimed at fusion of the affected joints.[446, 447, 1474, 3348] [But this was not always successful.—Ed.] Fusion of a Charcot's hip was successful.[447] Use of a compression apparatus for positive pressure and internal fixation was succesful for fusion of Charcot's knee joints.[1474, 3348] Posterior extra-articular fusion of the ankle was reported.[446]

Rheumatic Purpura (Schönlein-Henoch Syndrome)

Various terms again attached to this condition included "anaphylactoid purpura," "purpura rheumatica" and "acute vascular purpura."[2629, 2774] Two characteristic cases described by William Heberden under the title of "Purpureae Maculae," and published by his son William in 1802, had hemorrhagic skin lesions with gastrointestinal symptoms, joint pain, and hematuria.[2583]

This generalized disease was most commonly seen in children; edema of the face, extremities, and scrotum occurred in some patients. A preceding streptococcal infection, with hematuria and proteinuria similar to that of an acute nephritis, and occasionally with progression to a chronic nephritis, was the usual course, and was frequently characterized by persistence and by relapses. Purpuric skin lesions were essential to the diagnosis.[2312, 2774]

A hypersensitivity, allergy, or hyperimmune process of some type was proposed.[2312, 2531, 2774] One case due to a temporary sensitivity to chocolate was apparently proved by several recurrences after ingestion of chocolate, and a positive dermal test to chocolate. However, a few months later chocolate was taken with no recurrence, and dermal sensitivity tests were negative.[2531]

Of 64 cases, one third had elevated serum antistreptolysin titers, the same incidence as found in a control series of nonrheumatic children, and half that seen in children with rheumatic fever. *β hemolytic streptococci* of Group A were isolated in only one fourth of the patients investigated; there was no clear evidence that a streptococcal infection was an invariable causative factor.[464] Histologic findings of edematous red skin lesions showed an arteriolitis and fibrinoid necrosis, endothelial swelling, and eosinophilic infiltrations of tissues.[2629] [There is some question as to whether all of the patients described had Schönlein-Henoch purpura.—Ed.] Joint manifestations were sometimes absent but, when present, varied from arthralgia to severe, incapacitating arthritis in single or multiple joints, with local heat, redness, tenderness, and swelling.[2774] Joints were involved in 38 of 57 attacks suffered by 52 patients, an incidence of 67%. More than one joint was involved in 20 of 35 patients. Swelling of the periarticular structures was frequent, while effusions were rare. Migratory arthritis was infrequent. Most of the acutely involved joints subsided in two or three days, with or without treatment. Knees and ankles were most commonly affected; hips, wrists and elbows were less often involved.[464]

A five year old girl with Schönlein-Henoch purpura was successfully operated on for a complicating intussusception.[2961] Roentgenographic findings in two cases involving the small bowel were indicative of areas of transitory edema.[1321]

Serious neurologic complications were rare, but subarachnoid hemorrhage in two patients and convulsions in a third appeared during the course of Schönlein-Henoch purpura.[1884]

Renal involvement was not uncommon, but was only rarely persistent or fatal, although renal damage was the greatest danger of this condition.[760] Of 94 patients, 46 had some renal involvement. Two children died with chronic nephritis, and 13 left the hospital with persistent proteinuria and hematuria. Nine of the 13 later recovered completely. The remaining four had chronic nephritis. Five others who did not have renal involvement with their original illness later developed some asymptomatic impairment of renal function. [No renal biopsies were reported.—Ed.] ACTH and corticosteroids were used with apparent success in some patients,[606, 2774] but results were not always satisfactory, particularly in patients with renal complications.[2774]

Hemophilic Arthritis

The most common site of hemorrhage in hemophilic patients was into the cavities of large joints. Often such bleeding followed slight trauma, especially during spring and fall, when bleeding was more apt to occur.[1361, 1362] The knee, elbow, ankle, and hip were involved, in that order of frequency. Severe disability from marked deformities ensued in some cases. Pathologic features of hemophilic arthritis included thinning and erosion of cartilage, invasion of cartilage by granulation tissue, pannus formation, appearance of subchondral cysts, atrophy of subchondral bone, fractures, compressions, and flattening of articular surfaces. [These changes are not pathognomonic of hemophilic arthritis.—Ed.] In some cases, marginal excrescences or spurs were formed, and irregular increase in the width of epiphyses produced a characteristic knobbiness of the joints. In some cases the subchondral cysts were enormous. Advanced disorganization was the result of subchondral and intra-osseous hemorrhage that accompanied hemarthro-

sis. Erosion and cavitation of joint cartilages resulted from this bleeding.[756, 757, 1588, 2575, 2982]

Among the patients with classic hemophilia were some with a deficiency of antihemophilic factor (AHF). Others with similar symptoms, however, had biologically distinct abnormalities, including plasma thromboplastin component deficiency (Christmas disease), and combined abnormalities of the blood vessels and antihemophilic factors termed pseudohemophilia.[1362, 3081, 3354]

Treatment of hemophilic arthritis was both prophylactic and active. Preventive measures included careful handling of hemophilic infants, and curtailing of the activities of hemophilic children to protect them from abnormal [or even normal—Ed.] stresses and trauma. Patients were taught to recognize bleeding early, and to put the joint at complete rest whenever possible at the outset of the attack. Massive hemarthrosis required bed-rest, transfusions, ice packs to affected joints, and compression bandaging. Patients susceptible to massive hemarthroses needed to have access to a medical center where sufficient blood of all types was available for emergencies; frozen plasma could be used if the specific type of blood was not available. Removal of intra-articular blood by aspiration was often desirable. Spreading factors, such as hyaluronidase, were contraindicated in massive intra-articular hemorrhage. When bleeding ceased, active motion was instituted. In properly selected cases, surgical correction of some deformities was possible.[756, 757, 2575]

An antihemophilic globulin from bovine and pig blood was a hopeful development of research in this field. Efforts to increase potency and diminish antigenicity of this material were continuing.[1965]

Allergic Arthritis

Joint manifestations were the most common form of hypersensitivity reaction to penicillin. A serum sickness-like syndrome, with arthralgia, pruritus, urticaria, fever, proteinuria, and eosinophilia, characterized the delayed type of reaction. More severe and much less common reactions included exfoliative dermatitis and polyarteritis nodosa.[874, 1278] Acute anaphylactic reactions were more dangerous: many fatalities had occurred.[215, 874, 1278, 1973, 2060] Reactions to benzathine penicillin were relatively mild; a reaction rate of only 1.3% occurred among 12,858 naval recruits who received a single injection. The reaction was serious enough to require cortisone therapy in only one of 1,000 men injected.[1795] As noted in the Twelfth Review, effective treatment during the phase of arthralgia or arthritis called for the use of ACTH and adrenocorticosteroids, also epinephrine and antihistamine compounds.[1000, 2027] Penicillinase was also recommended.[207, 208]

A serum sickness-like syndrome followed administration of antivenom given for sea-snake bite.[2497] Various aspects of serum sickness were reported but not specifically described.[786, 964, 1119, 2784] [References to arthralgia or arthritis were meager. The subject is important, and worthy of more detailed attention.—Ed.]

Pharmaceutic Arthritis and Arthralgia

Acute, painful myostitis or arthritis among patients treated with hydralazine, described in detail in the Twelfth Rheumatism Review, was again reported. In

one case the hydralazine syndrome occurred within seven weeks of onset of treatment.[2519] Nearly 10% of patients under treatment with hydralazine had a positive L.E. phenomenon without having arthritis symptoms.[621] Of eight patients who developed signs or symptoms of rheumatoid or lupus erythematosus-like syndromes, four had positive L.E. preparations.[929] [See Section on Experimental Arthritis in Animals.—Ed.] All patients responded to withdrawal of hydralazine without further treatment.[929] [Recent reports suggest that these patients have a previous tendency to L.E.-like symptoms, and that certain abnormalities persist even though L.E. cells and symptoms seem to subside.—Ed.]

Alkaptonuria

This ailment, a rarely occurring "inborn error of metabolism," was still infrequently encountered, but increased interest in this condition was indicated by the fact that 24 publications dealing with alkaptonuria were available for this review. An extensive and detailed review of the literature was published.[1746] In advanced stages, patients with alkaptonuria often showed a most severe form of osteoarthritis, apparently induced as a by-product of the biochemical anomaly responsible for this condition. Similarities between the pathologic alterations in joints of this condition and the alterations encountered with primary osteoarthritis were striking. The three prime features were (1) alkaptonuria, the presence in urine of homogentisic acid; (2) alkaptonuric ochronosis, characterized by deposition of alkaptonuric pigments in ground substance of mesodermal tissues, especially those of the skeletal and cardiovascular systems and eyes, and (3) alkaptonuric arthritis, characterized by involvement of both axial and appendicular joints.[299, 432, 643, 1316, 1351, 1571, 1997, 2074, 2164, 2597, 2664, 2856, 3088, 3155] In one family, seven alkaptonurics appeared in four generations. The inheritance in this family conformed to the Mendelian recessive pattern.[1710] Three cases of ochronosis in siblings,[1757] and alkaptonuria in two sisters, were reported.[2410] Although earlier studies indicated that alkaptonuria was determined by a single recessive autosomal gene substitution, later studies showed direct transmission from patient to offspring, suggesting that alkaptonuria was inherited as a dominant gene substitution.[2134, 2147]

New studies on the biochemical anomaly of alkaptonuria reported absence of homogentistic acid oxidase in liver homogenate prepared from an alkaptonuric patient. Lack of activity was not due to the presence of an inhibitor or to absence of a co-factor. The basic defect appeared to be a failure to synthesize active homogentisic acid oxidase. All other enzymes involved in tyrosine oxidation had essentially the same activity in alkaptonuria and nonalkaptonuric human liver.[1794, 1795] A modified film spot test (Fishberg), suitable for estimation of homogentisic acid concentration in alkaptonuric urine, was described.[2911] The mechanism of pigment formation in alkaptonuric ochronosis apparently did not involve interaction between homogentisic acid, chondroitin sulfate, and molecular oxygen.[2148, 2164] Roentgenographic calcifications such as were found in intervertebral cartilages and ligaments were also found in tendon sheaths, bursal sacs, and synovial membranes. Calcified intervertebral cartilages, narrowing of the iliosacral synchondroses, and calcifications in tendons attached to the greater trochanter, quadriceps tendons and patellar tendons were other findings.[2333]

Other Types of Arthritis and Arthritic Syndromes

Intermittent Hydrarthrosis. The terms "hydrops intermittents articulorum," "intermittent hydrops," "chronic synovitis," "chronic allergic arthritis," "periodic benign synovitis," and "periodic disease" were sometimes used as synonyms. Criteria for selection of 47 cases from the records of 1,800 patients were (1) recurrence of joint symptoms at regular intervals; (2) complete freedom from signs and symptoms between attacks; (3) absence of a specific local causative factor, and (4) absence of a systemic reaction.[3261] The knee was most frequently involved, but any peripheral joint could be affected. Microscopic findings in the synovial membrane were similar to those of R.A., including proliferation of the synovial lining cells, edema of subsynovial tissues, and perivascular accumulations of plasma cells and lymphocytes in edematous villi.[3261]

Equally strict criteria produced nine cases from a total registry of 890,000, but in only one of the nine was the diagnosis certain; many suspected cases, when followed for a time, showed some other condition.[918] Three other cases were described; in two, remissions were apparently induced by corticosteroid therapy.[2033]

Most patients sooner or later developed rather characteristic findings of R.A.; the concept that "periodic benign synovitis" was a distinct entity was based on the assumption that the histologic reactions were nonspecific.[3261] [Careful clinical examination often reveals chronic synovitis of other, less symptomatic joints, and less regularity of the cyclic attacks than is usually presumed. It is more appropriate to regard intermittent hydrarthrosis as a variant of R.A.—Ed.]

Spontaneous remissions were frequent, and therapy was difficult to evaluate. No medical treatment was consistently effective. Corticosteroids were recommended but were not always effective.[2033, 3261] Synovectomy of the knee was of value in some severely affected cases.[3261]

Sjögren's Disease (Gougerot-Sjögren; Sicca Syndrome). The triad of arthritis, keratoconjunctivitis sicca, and salivary gland abnormality constituted Sjögren's syndrome. Lacrimal and salivary gland secretion was decreased or absent, and resulted in dryness of the ocular and oral mucosa. Skin, respiratory tract and gastrointestinal tract were sometimes involved. The literature was reviewed and cases were reported.[22, 1097, 1204, 2460, 3036, 3276] Arthritis ranged from mild early rheumatoid arthritis to severe, crippling forms, with typical deformities and nodules.[3276] [Although osteoarthritis is sometimes included because patients with Sjögren's syndrome are generally in the older age groups, and because the original descriptions did not clearly differentiate this point, it is currently suggested that the arthritis be limited to rheumatoid types.—Ed.] Parotid enlargement was recurrent. Lacrimal gland enlargement was unusual. Achlorhydria was often present. Disturbances in swallowing, with achalasia of the esophagus, were reported.[1097, 3276]

Lymphoid infiltration of salivary glands, with atrophic changes, sclerosis of lacrimal glands, and round cell infiltration about the accessory glands of the skin, were found. Perineural infiltrations and perivascular round cell infiltrations of connective tissue were also reported.[1097, 3036] Mucous membranes showed atrophy of the epithelium and thickening of the underlying connective tissue. Small blood vessels presented thickened sclerotic walls.[110]

Preliminary tests suggested that there might be antibodies to lacrimal and salivary glands in the serum of patients with Sjögren's syndrome.[1586] Ag-

glutination tests for rheumatoid arthritis were positive.[1097, 3276] The test was negative in one patient with Sjögren's syndrome not associated with rheumatoid arthritis.[1097]

Solutions of methylcellulose and cortisone were of value as eye drops in treatment of mild cases.[201] Sympathectomy, vitamins, estrogens, androgens, pituitary implants, and x-ray treatment have had their advocates.[3276] ACTH and corticosteroids usually relieved symptoms of arthritis and, though their effect on the lacrimal and parotid glands was equivocal, their use was recommended.[22, 1097, 1204, 2460, 3276]

Reticulohistiocytosis. Reticulohistiocytoma with multiple skin lesions and deforming arthritis of varying degrees of severity was reported as a definite entity of unknown etiology.[1577, 2180] Synovial membranes as well as the skin were involved; biopsy of synovia and bone in one patient revealed giant histiocytes. This condition was apparently not a neoplasm or one of the xanthomatoses, and was not due to a disturbance in lipid metabolism.[2180] In one case, over a 14-year period, extensive bone resorption, especially of the phalanges, resulted in almost complete destruction of distal and middle rows of phalanges, with disappearance of interphalangeal joints. The fingers were a third their normal length, and folds of redundant skin were invaginated into each joint area in telescope fashion.[1577]

Tietze's Syndrome. The literature was reviewed and cases were reported.[1633, 1693, 1736, 2551, 2649] "Thoracochondralgia" was suggested as a descriptive term, in preference to the eponym.[2649] [But because of inflammation of cartilage, "thoraco-chondritis" or something similar would be more appropriate.—Ed.] Sternoclavicular swelling was included in this category, although the original description was that of painful, nonsuppurative swelling of the costochondral cartilages.[1693] It was important to recognize the possibility of this condition in the differential diagnosis of chest pain. Although the course might be prolonged, it was generally tolerated if the patient understood the nature of the disorder.[3258] Suggested causes included external trauma, unaccustomed mechanical stress, microtrauma at the site of the insertion of the interarticular costosternal ligament, and contracture of ligaments with forward buckling of the cartilage.[1641] Diagnostic criteria consisted of (1) the presence of a painful, tender mass involving at least one of the costosternal junctures; (2) evidence that this mass was a distinct enlargement (not merely a prominent joint); and (3) absence of clear-cut evidence that could establish another definite etiologic diagnosis.[881, 1633] Costochondral cartilages of the upper ribs, most often the second, were involved. Pain and tenderness were the usual complaints. Intensity of pain varied from mild to severe; exacerbations with deep breathing, cough, and sudden movements were common. Pain was aggravated by anxiety, worry and fatigue. The fusiform or spindle-shaped swelling of one or more upper costochondral junctions usually disappeared in from 10 days to 10 weeks. There was no redness of the overlying skin.[1633, 1641, 3259] [But there often is localized heat over affected areas. —Ed.]

Swelling or edema of the perichondrium and soft tissues was found in some biopsies. The cartilage usually appeared to be prominent, but whether this was due to actual enlargement or to forward angulation was not clear. No specific histologic changes were found. There was no evidence of new growth of cartilage, but in one case findings were compatible with granuloma.[1641]

There was no specific therapy. Reassurance, local heat, and analgesics usually sufficed. Infiltration with procaine hydrochloride solution, x-ray therapy, or diathermy was used. Hydrocortisone solution injected into the lesion gave prompt relief of pain and decreased the swelling.[881, 1633, 1641, 1736] Successful treatment with oral prednisolone was reported in one patient.[2094] Synovial excision was reported, but should be unnecessary.[918]

Behçet's Syndrome. Involvement of the nervous system in association with the triple symptom complex of recurrent ulcers of the mouth and genitalia and relapsing iritis was reported with increasing frequency.[931, 2336, 3190, 3298, 3322] Prognosis was much worse in cases with nervous system involvement; almost half had proved to be fatal.[931]

Ulcers in the mouth were usually small, and appeared as open lesions or occasionally started as submucous nodules. They often coalesced to form irregular lesions up to 1 cm. in diameter, and sometimes extended into the pharynx and esophagus. They tended to appear in crops and were intensely painful, interfering with speech and nutrition. Genital ulcers were larger and usually also quite painful. Ocular involvement was at first a unilateral iritis, but with repeated attacks both eyes became seriously involved, with development of hypopyon, retinitis, and retrobulbar neuritis. Intense pain and blindness frequently required enucleation. Erythema nodosum, pyoderma, acneiform and pustular lesions, and large, indolent ulcers were reported. Muscle and joint pain was common, but definite joint swelling and arthritis were unusual. Fever was usually present during acute episodes.[3190]

Neurologic involvement was relapsing in nature, with remissions marked by improvement and even disappearance of signs between episodes. Predilection for brain stem localization and the tendency for motor signs to be more frequent than sensory disturbances were other characteristics. Episodes often suggested a recurrence or spreading involvement at the same site, or sometimes indicated an entirely new location of the lesion.[3298]

Patterns of nervous system involvement were identified as (a) brain stem syndrome, (b) a meningomyelitic syndrome, and (c) an organic confusional syndrome.[2336] Headache was the presenting symptom in almost all patients.[3190] Cerebrospinal fluid usually showed pleocytosis and increased protein.[3298]

Postmortem examination of one patient revealed (1) small focal softenings in both gray and white matter, largely confined to the midbrain, pons, and medulla, with occasional small areas of perivascular demyelination, and (2) perivascular cuffing, most obvious in the brain stem, and also apparent in the insula and spinal cord. These perivascular infiltrations were mainly related to veins. Nerve cell changes were slight, and no inclusion bodies were found. A virus was isolated from the eye and brain of this patient.[931] Findings were similar to those in some cases of herpes simplex encephalitis, a direct cerebral invasion of the virus, and also to cases of encephalitis following secondary vaccination, largely a sensitization effect.[3298]

A case was reported of a 17 year old youth hospitalized because of recurrent episodes of tenderness, redness, and swelling of the ankle, leg, and thigh, considered to be an unusual form of thrombophlebitis migrans. Ulcerations of the mouth and scrotum had been recurring for three years.[495] A 34 year old woman developed a severe but temporary arthropathy involving multiple joints about a month after the onset of genital ulcers. A diagnosis of R.A. was initially made,

but all joint findings subsided and there were no residual deformities.[1906] The histologic examination of an enucleated eye showed a widespread inflammatory reaction, not only in the uvea and the retina but also extraocularly, in the episclera and in the extraocular muscles. The inflammation was predominantly perivascular.[372]

Erythema Multiforme (Stevens-Johnson Syndrome). Case reports with reviews of the literature were published.[21, 407, 1422, 1854, 2168, 2297, 2717, 2757, 2781, 2795, 3027] Erythema multiforme was considered to be probably allergic, or a hypersensitivity reaction to pharmacologic or bacterial excitants;[2757] Stevens-Johnson syndrome was one of the "major" variants of erythema multiforme, usually due to an infection of some type.[3027] The diagnosis rested on the presence of ulcerative or exudative erythema multiforme lesions of the skin; the mucous membrane of the alimentary canal, respiratory system, genitourinary tract or eyes[2168, 3027] also were often affected. Nails were sometimes shed. Joint effusions occasionally occurred. Painful mucous membrane lesions of the mouth and pharynx made swallowing difficult, and intravenous feeding was frequently necessary.[2168] Pneumonitis that was radiographically, serologically and clinically indistinguishable from primary atypical pneumonia occasionally occurred.[2757] Erythema multiforme, with painless lesions limited to the oral cavity, was reported.[1897] [The mucosal lesions of so-called Stevens-Johnson syndrome are characteristically painful. The painful, crusted skin lesions and mucosal ulcers covered with membranes are features that distinguish Stevens-Johnson syndrome from Reiter's syndrome. In the latter, the skin and mucosal lesions are painless.—Ed.]

ACTH or corticosteroids were usually effective therapy, but were not advised for those with mild involvement.[407, 1422, 1854, 2168, 2781] Four fatalities occurred in spite of corticosteroid therapy.[2297, 2795, 3027] Another patient died while being treated with ACTH and corticosteroids, probably from an infection.[2795]

Temporomandibular Joint Pain, Including Costen's Syndrome. Dysfunctions of the temporomandibular joint apparently were the basis for many cases of atypical facial pain, as was stressed by Costen in 1934. Injection of hydrocortisone into the joint, with relief of pain for up to three or four weeks, proved to be a valuable confirmatory test and made diagnosis more reliable. Three types of discomfort were recognized: (1) arthritic, (2) muscular, and (3) neuralgic. Pain in the ear, facial pain, impaired hearing, and tinnitus were not common, but were associated with arthritis. Malocclusion, with overstretching and spasm of the pterygoid and temporal muscles, caused pain in the region of these muscles, and deep behind the eye, or down into the tonsillar fossa or throat. Patients with neuralgic pain had mild, constant aching pain in the cheek secondary to severe flashes of neuralgic pain in the throat, ear, or lateral side of the tongue. Pain was sometimes burning or tingling in character. Chewing or pressure over the joint often initiated pain.[281, 2539] Of 100 patients in whom there was excessive loss of vertical dimension as a result of tobacco chewing only four had any complaints; it was therefore assumed that loss of this dimension was rarely a factor in production of temporomandibular joint syndrome when cusp interference had been eliminated.[2231]

Restoration of occlusion, with simultaneous or even contact at the correct vertical dimension, or an occlusion that did not direct mandibular movement to the detriment of the joint, was the basis for dental treatment.[2624] Arthroplasty, with interposition of tantalum foil, was reported for temporomandibular anky-

losis.[1201] Local injection of hydrocortisone gave relief of symptoms within a few hours, and this lasted for three or four weeks or longer.[281]

Postcommissurotomy Syndrome. Recurrent febrile episodes, coming on two to four weeks after cardiac surgery, with fever, chest pain of a pleuropericardial nature, pleural effusion, pneumonitis, and polyarthralgia constituted the postcommissurotomy syndrome.[923, 1527, 1971, 2339] Since this syndrome also followed surgery on congenital heart lesions, it might better be called the "postpericardiotomy syndrome,"[1527] or the "postcardiotomy syndrome" in patients with rheumatic heart disease. Myalgia and arthralgia occurred occasionally, but arthritis was rare[1527] or did not occur.[1828] In six of 33 patients, polyarthralgias were of a nonmigratory type. Fingers, wrists, elbows, ankles, and knees were painful, but no swelling, redness or increased warmth was noted. Joint pain was due[1971] or not likely due[1527] to reactivation of rheumatic fever, but three patients had exacerbations of rheumatic fever, with peripheral joint pain, fever, elevation of the erythrocyte sedimentation rate, and prolongation of the P-R interval. This arthralgia responded promptly to cortisone therapy. One patient had multiple subcutaneous nodules over the abdomen and thorax, varying in size from a few millimeters to 3 to 4 cm. They were firm and discrete, lacked warmth, and were not tender or painful. One biopsy showed a subcutaneous granulomatous nodule with minimal panarteritis; another biopsy showed an artery with changes similar to those seen in periarteritis nodosa.[816]

ACTH for two days preoperatively and eight to 10 days postoperatively decreased the incidence of this syndrome in patients undergoing mitral valvuloplasty. Cortisone had a definite suppressive effect on the condition, and was superior to salicylates, Pyramidon, and antibiotics.[816]

Temporal Arteritis. Clinical manifestations consisted of severe, throbbing head pain, swelling of the face, redness of the skin over the temporal arteries, hyperalgesia of the scalp, and visual loss.[681] Ocular involvement occurred in almost half of the affected patients. Blindness or very severe impairment of vision was common.[222, 267, 883, 2790, 2791, 3191] Temporal arteritis, with the exception of ocular manifestations, was reported to be a self-limiting and benign condition. Isolated segments of the temporal arteries and occasionally other arteries appeared to be larger than normal, and were often nodular, or appeared to be solid cords with little or no lumen. Histologically there was narrowing or occlusion of the lumen, due to intimal proliferation, with or without thrombosis. Localized periarteritis and mesarteritis were also present. Focal necrosis of the media, with replacement by granulomatous tissue containing numerous foreign body giant cells, was found. Eosinophilic infiltrations were uncommon, and aneurysmal dilatations were rare.

Treatment to prevent visual loss and progression of the arteritis was the immediate and primary consideration. ACTH, cortisone, or related corticosteroids controlled the arteritis and, in adequate doses, prevented progression or loss of vision. Dosage was usually kept high, above the equivalent level of 100 mg. cortisone daily. Phenylbutazone was reportedly effective,[271] but the prognosis with corticosteroid therapy was better than with other treatment.[221, 222, 267, 883, 2790, 2791]

Transient Synovitis of the Hip. This condition, called "transitory arthritis," "coxitis serosa," "transitory coxitis," "coxitis fugitive," "coxitis serosa seu simplex," "observation hip," and "irritable hip," was probably "the most common affection of the hip in children." Onset was abrupt or insidious in a child between three and 10 years old. Limp and unilateral pain in the hip, thigh, or knee were the usual complaints. Recovery occurred in a few days to a few weeks, and no residual damage occurred.[489, 1031, 2609, 3170] Roentgenograms often showed perifocal soft tissue swelling of the capsule and bulging of the obturator internus, iliopsoas, and gluteus minimus muscle shadows.[2485]

Response to bed-rest and salicylates was usually satisfactory. Occasionally trac-

tion was used.[489, 1031, 2485, 3170] ACTH and cortisone gave gratifying results.[2615] [Corticosteroid therapy hardly seems justified in the treatment of this generally ill-defined and self-limiting condition. Possible masking of a more serious lesion would also make steroids inadvisable.—Ed.]

Arthritis of Ulcerative Colitis. Arthritis, present in 40 of 245 patients (16%) [154] and in 17 of 131 surgically treated patients (13%) was "the most common remote complication" of ulcerative colitis. Large joints, especially knees, were usually affected. Arthritis often improved after colectomy, but sometimes had its onset after surgery if any part of the large bowel remained. There were three deaths among the 17 patients who were operated upon; only one of the remaining 14 failed to recover from arthritis following surgery, and this patient had suffered from arthritis for four years before operation.[401] Arthritis, as well as erythema nodosum and pyoderma, was relatively more common in patients treated with supportive measures alone, and relatively more frequent in patients with right-sided colitis.[154]

Erythema Nodosum. Erythema nodosum was characterized by lesions with a fairly uniform morphology and a characteristic course, and was probably due to a "hypersensitivity" reaction. A variety of infections and chemical agents, as well as local trauma, led to its occurrence.[1663, 2126, 3026] The condition was described in association with tuberculosis, rheumatic fever and other streptococcal diseases, coccidioidomycosis, histoplasmosis, syphilis, leprosy, trichophytosis, meningococcemia, sarcoidosis, and drug reactions, especially a sensitivity to sulfonamides.[1337, 1557, 1663, 2126, 3026] It could still have an independent etiology.[2126] Associated arthralgia or arthritis, described as pain, swelling, tenderness and redness of knees, ankles, elbows, and wrists, was not unusual.[1557, 1663, 2291, 3026] It was more common in females, and the lesions were almost always on the anterior aspects of the legs.[1663] [Thighs and upper extremities are also occasionally involved.—Ed.]

Lesions of erythema nodosum occurred in six of 71 patients with ulcerative colitis. Four of the six also had "arthralgia," and the painful, swollen, and warm ankles characteristic of arthritis. Lesions appeared at a time when the ulcerative colitis was active.[1663] Twenty-seven patients with erythema nodosum had histologic evidence of sarcoidosis. Seventeen (63%) had an associated polyarthritis which involved chiefly the knees, ankles, wrists, and elbows. Movement of joints was limited by pain; joint effusions were not observed. The polyarthritis subsided completely in every case. In 24 of the 27, roentgenograms of the chest showed bilateral hilar lymphadenopathy. This disappeared in all; later, five had transient, diffuse pulmonary mottling.[1557] A seven year old girl with a family history of tuberculosis had eight intermittent episodes of erythema nodosum over a 17-month period. Pain in the right shoulder occurred during one episode, but no definite arthritis was described.[1337] An eight year old American Indian boy had erythema nodosum associated with primary tuberculosis.[3026] Pulmonary histoplasmosis accompanied by erythema nodosum and arthralgia was reported in a 13 year old girl.[2291]

Erythema nodosum leprosum was common among lepromatous patients of Ghana; there were 906 episodes in 174 patients, and one patient had 31 episodes during a four-year period. Lesions were usually painful, and were sometimes accompanied by bone and joint pain. Ulnar and peroneal neuritis were also often associated. No correlation between stage of treatment and frequency of the erythema nodosum lesions was found.[3016]

Rubella Arthritis. A self-limiting polyarthritis occurred as a complication of rubella, or German measles, in 10 females. The small and medium-sized joints of hands, wrists, and ankles were affected for about a week. The latex test was positive in nine of the 10 with arthritis, and negative in five of seven patients who had rubella without arthritis. This high incidence suggested that R.A. was caused by a viral infection in a susceptible host.[1581] [There is little evidence for this possibility. Rather, it might be suggested that these patients had an episode of R.A. precipitated by the infectious disease.—Ed.]

Sickle Cell Disease. Rheumatic pain in bone and joints was the most characteristic single symptom of sickle cell disease. Roentgenographic findings of marrow hyperplasia appeared usually in flat bones, and consisted of decalcification, thinning of the cortex, and widening of the marrow cavity. In the long bones, such changes were rare, but x-ray findings of hypoxia consisted of thickening of the cortex, narrowing of the marrow cavity, and a bizarre coarsening of the trabeculae. Localized areas of thrombosis, of varying size and number, appeared to be radiolucent when necrotic bone was replaced by hyaline or fibrous tissue or, more commonly, were radiopaque when the area of necrosis had become densely calcified. Entire ossification centers were sometimes involved. Aseptic necrosis of the capital femoral epiphysis led to the deformity of Legg-Perthes' disease. Sickle cell dactylitis, characterized clinically by painful swelling of the hands and feet, and lasting for several weeks, with regression to normal, presented radiologically with periosteal proliferation about the shafts of some of the metatarsal, metacarpal, or phalangeal bones. Cystlike areas of destruction also appeared in the involved bones. Skull changes were of interest. This condition occurred in children, was not associated with fever, and was not influenced by antibiotics. The bones gradually regressed to normal.[498]

Disseminated Lipogranulomatosis (Farber's Disease). A single case of this disturbance in lipid metabolism was reported. Symptoms appeared in this boy immediately after birth, and consisted of vomiting, hoarseness, and periarticular changes, with swelling about joints and a tendency to contractures. At four months he developed swelling and redness of the finger joints and knees, with flexion contractures of the fingers and knees. At 10 months he developed subcutaneous granulomas or nodules on the scalp and over the ribs, and later many of these developed over and adjacent to joints. Microscopically, these consisted of sclerotic connective tissue with a moderate number of blood vessels and groups of irregularly formed, large, pale, light cells with foamy, granular cytoplasm. Generalized lymphadenopathy, hepatomegaly and cardiomegaly were other findings. This condition was believed to be a primary lipoid metabolic defect and not a reticuloendotheliosis.[3409]

Scurvy. Hemarthrosis of the right knee in a 63 year old woman was due to scurvy. Less than 1% of the loading dose of ascorbic acid was excreted in eight hours.[1160] [No gamma globulin values were given.—Ed.]

Hodgkin's Disease, Leukemia, Multiple Myeloma. Attention was again called to the osseous and articular manifestations of Hodgkin's disease, which most often involved the spine, and to the joint symptoms of acute leukemia of children. Bone involvement in multiple myeloma was quite common, but joint involvement alone was unusual. Amyloid substance was found in the articular and periarticular structures at postmortem examination.[2340]

Miscellaneous. Two patients with reticular sarcomatosis presented with pain in the joints, and were at first thought to have acute rheumatic fever.[3001] Three cases of biliary cirrhosis with hypercholesterolemia and bone lesions were reported. Subchondral bone lesions led to collapse of the femoral head, with secondary osteoarthritis and hip pain in two of the patients. Mechanical weakening due to replacement of subchondral bone by foam cells was an important factor.[92]

Under the title of "peripatetic rheumatic hydroarthrosis," the case was reported of a man who, over a 20-year period, had multiple episodes of massive painful joint effusion, with erythema of the overlying skin, nausea, and vomiting. His symptoms always subsided rapidly, within a few hours. No residual findings were reported. For the first 16 years, attacks occurred irregularly, every five or six weeks, in either a knee or an elbow, rarely in an ankle. During the last four years he had taken two cortisone tablets at the first evidence of nausea and had not developed a typical attack.[1727] [This description suggests periodic disease of Reiman.—Ed.]

Four patients with pyoderma gangraenosum associated with rheumatoid arthritis were reported.[131] [No gamma globulin values were given.—Ed.]

The Painful Shoulder

Definitions. Sharp delineation and increasing general agreement on terminology continued, with the differentiation and designation of the intrinsic extra-articular painful shoulder syndromes as calcific tendinitis, bicipital tenosynovitis, adhesive capsulitis, musculotendinous (cuff) lesions, especially tears, and the shoulder-hand syndrome.[31, 1035, 1066, 1091, 1127, 1297, 1552, 1576, 1739, 1790, 1817, 2130, 2171, 2172, 2208, 2270, 2445, 2446, 2447, 3067] This trend in classification of the extra-articular shoulder disorders was noted in the Eleventh and Twelfth Rheumatism Reviews (*1k,l*). General division of causes of the painful shoulder as "intrinsic" and "extrinsic" also continued to be favored. Extrinsic sources receiving attention consisted largely of the cervical disc disorders, cervical osteoarthritis, thoracic outlet syndrome, whiplash injuries, cervicobrachial neuralgias, and other well defined entities.[44, 343, 390, 444, 722, 928, 1020, 1260, 1770, 1938, 2097, 2189, 2190, 2204, 2245, 2253, 2544, 2779, 3145] Soft tissue lesions producing pain and stiffness in the shoulder region were classified by Bates as follows: *Group I,* those which produced shoulder and neck pain; *Group II,* those which produced shoulder pain only; *Group III,* those which produced shoulder pain with radiation to the extremity, including the hand.[940]

Anatomy. The complexity of the problem of the painful shoulder was explained by the anatomy of the structures which support the upper extremity.[1127] The brachial plexus, the shoulder joint, and the arm were all suspended from the cervical part of the spinal column by muscular and ligamentous structures. The only bony contact was at the sternoclavicular joint, the clavicle acting as a boom to which many of the other structures were attached, and as a prop to keep the shoulder in a position away from the wall of the chest. The head of the humerus moved below a vault formed by the apophysis of the coracoid process, the coraco-acromial ligament, the acromioclavicular articulation, the acromion, and the deltoid.[2130] It was fixed in the glenoid fossa by the muscular cuff, composed from front to back of the following muscles: subscapularis, supraspinatus, infraspinatus, teres minor (the four short rotators), and the long head of the biceps. These muscles fused into one common tendinous band (cuff) which joined with the capsule close to its insertion into the anatomic neck of the humerus.[2270]

Arthrography extended nonoperative diagnostic resources and was capable of demonstrating capsular tears and joint space encroachment.[1699, 2130] "The remarkable thing about the shoulder is that it ever worked at all and that pain was ever absent."[625]

Clinical Syndromes. Basic descriptions of the intrinsic shoulder syndromes were given in the preceding Rheumatism Reviews and will not be repeated. No noteworthy additions were reported.

Calcific Tendinitis. Degenerative supraspinatus tendinitis, reportedly the most frequent cause of shoulder pain,[31] seemed to be replacing the old terms of "bursitis," "subdeltoid" or "subacromial" bursitis. Of 250 asymptomatic shoulders in 80 women and 45 men, residents of a home for the aged, 55 showed varying amounts of calcific deposit in the rotator cuff;[30] 14 of these were in men and 41 in women, and only nine of these patients had pain. The explosiveness, tendency to spontaneous abatement, ready response to a wide variety of effective (and often innocuous) therapy, the underlying microtrauma, the frequent presence or lack of calcium, and the descriptive pathology of acute tendinitis again

were well documented. Progression to a chronic stage of smoldering activity and the concomitant resistance to therapy were noted.[31, 1066, 1127]

Bicipital Tenosynovitis. This disorder presented a difficult problem: it had a predilection for individuals past 40 years of age, often as a precursor to, or extension of, adhesive capsulitis. A 40 to 50% spontaneous remission rate was reported, as well as a decided tendency to chronic disability.[31, 1127, 1297, 1699] Two diagnostic tests described were (a) Yergason's sign (the presence of pain on active contraction and relaxation of the biceps when the shoulder is held by the side), and (b) Lippmann's sign (production of pain when the patient actively tightens the biceps with the elbow flexed to 90° while the examiner seizes the tendon just below the bicipital groove, pulls it to one side, and lets it go). Neither was of great value.[625]

Adhesive Capsulitis. This condition, frequently called "the frozen shoulder" or "periarthritis," remained the supreme problem of the painful shoulder in regard to prolonged disability. It frequently developed in the wake of the other intrinsic shoulder disorders, and in many instances followed extrinsic shoulder joint disease.[746, 1127, 1297] Concomitant calcium deposits at the shoulder occurred in 20 to 43% of cases.[1127, 2130] Adhesive capsulitis was considered to be an "idiopathic" condition in about one third of the patients.[1127] [Actually, the absence of a demonstrable "cause" makes the majority of these conditions appear to be "idiopathic."—Ed.] The prognosis for pain relief was good, but for disability it was poor in the absence of therapy [and often in spite of it.—Ed.].[1127, 1297, 1699, 2446]

Musculotendinous Lesions (Chiefly Tears). Emphasis was placed on the predominance of asymptomatic tears, which increased with age,[1066] on the good prognosis for nonoperative healing of small tears, on the feasibility of surgical repair as long as four to six weeks after injury, and on the value of arthrography of the shoulder in diagnosis of its lesions.[1066, 1127, 1297, 1699]

Scapulocostal Syndrome. A symptom complex involving unilaterally the shoulder and the superior portion of the scapula, with radiation of pain patterns into the head and neck, the deltoid muscle, and the arm and hand, was termed the "scapulocostal syndrome" by A. A. Michele in 1950. It was a common cause of pain in the shoulder area; 150 patients in private orthopedic practice were seen during a three-year period.[2067] All had "trigger points" at the superior vertebral angle of the scapula or at the base of its spinous process. Symptoms varied from five years' to one day's duration, with an average of approximately eight months. Relief was obtained in 90% of these patients with 1% procaine, followed by 2% Intracaine (β-diethylaminoethyl p-ethoxybenzoate) in oil. [We doubt if this entity exists, and do not accept this remarkable claim of results.—Ed.]

Pathogenesis. The pathogenesis of rotator cuff tendon lesions was discussed mainly in terms of descriptive pathology. Microtrauma and degeneration of the tendinous tissue, with precipitation of calcium due to local factors, were the common precursors of acute tendinitis.[31, 1066, 1127] [Why such damaged tendons explode intermittently with aseptic inflammation is still enigmatic in the apparent absence of overt trauma in many of the patients.—Ed.] Bicipital tendinitis and tenosynovitis rated a special status, because the shoulder synovialis served as a sheath for the tendon and logically could be the vehicle for extension of inflammation from the joint itself, or, conversely, to the joint by continguous spread from an initial tenosynovitis. The frequent association of these two mechanisms implied a close relationship.[31, 1297, 1699, 2446] The pathology of adhesive capsulitis was

similarly described, with small variations, regardless of the nature of the associated (and probably precipitating) factors.[1127, 1699, 2266, 2446, 2959] Two theories received chief emphasis: the enhancing effect of immobilization on the inherent tendency of joints with latent or overt pathology to stiffen; and the possibility that the condition represented a local form of reflex dystrophy. Preventive exercises were effective in reducing incidence in known precipitating illnesses.[628, 2230, 2636, 2959]

Differential Diagnosis. This required awareness of the disorders producing painful disability of the shoulder and of criteria for their diagnosis.[2113] Precise localization of pain and presence of weakness on resisted movements observed during clinical examination of the different painful shoulder syndromes were correlated and listed as valuable diagnostic aids.[712] Arthrograms,[1699] electromyography,[1086] special radiologic examinations,[343, 2204] and venograms were helpful.

Treatment of Intrinsic Shoulder Conditions

Acute Tendinitis. Treatment of this condition was summarized in previous Rheumatism Reviews. It was not the subject of major changes, aside from variations in emphasis. Basic measures consisted of rest, analgesics (including phenylbutazone), and hot or cold applications. "Specific therapy" varied, but all methods provided remissions in 80 to 95% of cases. Local procaine-hydrocortisone injections (with or without multiple puncture and irrigation) continued to be favored.[1066, 1162, 1335, 1573, 1817] Ultrasonic[1041, 2268, 2391] and x-ray therapy were well regarded.[106, 291] Diathermy and systemic corticosteroids received little comment. Vitamin B_{12},[1739] Priscoline[1035] and magnesium sulfate iontophoresis,[2245] acromionectomy,[31] and evacuative surgery (for calcium deposits)[1066] were satisfactory treatments. [The actual value of some of these remains to be confirmed. —Ed.] Shortening of the pain period in the acute phase to from 24 to 48 hours, and good functional result in from seven to 10 days, along with the need to do something dramatic, seemed to be the main objectives of these methods.[106] However, progression to chronic stages often occurred despite even energetic use of these treatments while the process was acute. "Selected patients" responded to any of the above "specific" measures, added to physical therapy and time. Nevertheless, adhesive capsulitis, or chronic or intermittent tendinitis, still developed in some patients.[106, 1066, 1162, 1335, 1573, 1817]

Bicipital Tenosynovitis. Varied responses to therapy were described; 40 to 50% recovery was reported, regardless of the treatment used. During the acute stage, procaine-hydrocortisone injections gave impressive results.[1127, 1162, 1817, 2130] X-ray therapy and systemic corticosteroids were effective at times.[1127, 2171] Abduction splinting was recommended during the acute stage.[31]

Adhesive Capsulitis. Prevention was of major concern whenever a known provocative factor was present. Prompt treatment of the activating factor and "prophylactic" shoulder exercises were advocated.[2636, 2959] Once the inflammatory or stiffening process had begun at the shoulder, prompt therapy was needed to diminish the incidence of the resulting "frozen shoulder."[2072, 2636, 2959] The use of systemic corticosteroids, infiltration of local trigger points with hydrocortisone and procaine, and injections of hydrocortisone into the subcoracoid, subacromial and/or subscapular portions of the joint, combined with careful exercises, were advocated.[2083, 2130, 2636, 2959] When the capsulitis was part of the classic shoulder-hand syndrome, corticosteroids or stellate ganglion blocks were

most effective.[2959] Manipulation and surgery were avoided during the acute phase,[1127] but produced good results in restoring range of motion (up to 95%) in the "burned out" stage, when disability due to restriction of movement, not pain, was the major complaint.[1335, 2445, 2446, 2447]

Musculotendinous Tears. Within four to six weeks of onset, simple tears did well merely with rest of the extremity; larger tears required surgery. Functional results were good.[1127] Intermittent symptoms at the shoulder nevertheless resulted from these old lesions undergoing the cumulative stress and deterioration of aging.[1127]

Reflex Dystrophy, Including the Shoulder-Hand Syndrome

It was reiterated that the shoulder-hand syndrome, Sudeck's atrophy, posttraumatic osteoporosis and other variously termed reflex sympathetic dystrophies of the shoulder and upper extremity represented essentially similar forms of an abnormal neurovascular response.[2208, 2602, 2636, 3340] [This subject was summarized in the Ninth and Tenth Rheumatism Reviews (1*j*, *k*).—Ed.]

The Shoulder-Hand Syndrome. This condition was first described in detail and given its name by Steinbrocker in 1947. The syndrome was not widely recognized as a distinct clinical entity and a common cause for disability of the shoulder and hand. The cardinal symptoms were listed as severe pain causing limited motion of the shoulder, and preceded by, occurring simultaneously with or followed by pain, vasomotor disturbance, and swelling, with limited flexion of the hand and fingers of the same extremity. Patchy osteoporosis of the carpus, the head of the humerus, and sometimes the fingers occurred in 70% or more of cases.[2208, 2602] The three stages of the clinical course continued to be described.[820, 2602] In *Stage I,* the initial three to six months after the onset of painful shoulder, disability and/or hyperemia, loss of skin lines, nonpitting edema, and pain in the hand, the hand was pink or red, later cyanotic or pale, and the grip was weak. Trophic nail changes might be present. X-rays might reveal spotty decalcification of the wrists, fingers, and upper humerus. In *Stage II,* there were pain, stiffness, and limited motion of the involved extremity. The hand was cold, its skin thin and atrophic. Muscle atrophy was present, and the bone changes seen in Stage I were exaggerated. This stage also lasted from three to six months. In *Stage III,* digital contractures developed, with irreversible changes in the hand and permanent limitation of mobility of the hand and fingers, and occasionally of the shoulder. The skin of the hand became smooth, then glossy, with atrophy of subcutaneous tissue and intrinsic muscles. Osteoporosis of the whole extremity might result. The fingers might be fixed in flexion due to contraction of the palmar fascia similar to Dupuytren's contracture. [All patients with this type of upper limb dystrophy do not necessarily pass through these stages. These changes are capable of reversal and recovery at any point in their course, short of Stage III.—Ed.]

The designation "shoulder-hand syndrome" was sometimes used for pain and/or stiffness appearing after myocardial infarction, without regard for the well defined clinical features constituting the syndrome.[846, 1127] [Use of loose diagnostic criteria led to an overly optimistic prognosis.—Ed.]

Reduction in the frequency of the shoulder-hand syndrome as a complication of acute myocardial infarction was observed.[2636] Whereas the incidence was formerly 10 to 20% of all cases, it was infrequent today because of the liberaliza-

tion of restrictions in activity. [No data were presented to support this opinion. —Ed.]

Attention was called to the occurrence of this disability in patients with cerebral lesions, particularly cerebral vascular accidents.[2208, 2602] Early recognition and therapy prevented irreversible contractures and disability.

Sudeck's Atrophy. This was a post-traumatic neurovascular dystrophy which was responsible for painful disability of a limb.[2286, 2408] Causalgia was distinguished from Sudeck's atrophy and other reflex disorders of the extremity by the following characteristics: (1) burning pain of causalgia type, (2) exquisitely sensitive response to environmental stimuli, and (3) symptomatic responsiveness (at least temporarily) to sympathetic block.[3297] Absence of shoulder disability was a remarkable feature in 37 cases of Sudeck's atrophy of the hand.[2408] In nearly all of these patients, trauma was a precipitating factor.

Pathogenesis. Current theories regarding the specific or combined role of the "internuncial pool," psychogenic factors, and "inactivity" of the affected limb were discussed.[1275, 2208, 2636] A wide variety of precipitating conditions, involvement of the sympathetic, parasympathetic and motor pathways, lack of segmental distribution, and therapeutic success from sympathetic block gave support to the "internuncial pool" theory.[2602] [The cause of this symptom-complex is still not known. It is a rarity today.—Ed.]

Prognosis. The shoulder-hand syndrome had a good prognosis, with or without treatment, and was often self-limited[846] or spontaneously resolved, but the best results were obtained by early recognition and active treatment.[2208, 2602 2636] Without treatment the outcome was unpredictable, and changes more often became irreversible.

Treatment. Aims of treatment were the relief of symptoms, earliest possible restoration of function to the extremity, and prevention of residual effects.[88] "Adjunctive therapy" consisted of rest of the part for acute or hyperacute symptoms, various analgesics, sedatives or relaxants, physical therapy, and psychotherapy in some cases. With control of pain, graduated passive and active exercise of shoulders and hands was employed.[88, 846, 2208, 2408, 2602, 2636] Sympathetic ganglion (stellate) blocks and systemic corticosteroids were treatments of choice. Adrenocorticosteroids were generally used at the dosage levels commonly used in rheumatic disorders. Following initial improvement, the dose was tapered.[2208, 2602, 2636, 3125]

Prevention. The importance of prevention of reflex neurovascular disorders in conditions known to predispose to them, such as trauma to the hands and feet, and cerebral and myocardial vascular occlusions, was emphasized. Alertness for early signs of neurovascular pain and reactions, passive and active graded exercises of the extremities, local infiltration of tender points at the shoulder with procaine or hydrocortisone, and the avoidance of casts and manipulation of parts in the presence of atypical pain or peripheral vasomotor signs were advocated as prophylactic measures.[88, 2208, 2636] Since their introduction, decrease in the frequency of the shoulder-hand syndrome following myocardial infarction was reported.[2636] [It may be too early to evaluate the effect of therapy, but most of us are seeing fewer patients with this condition since active exercises have been instituted as part of the treatment of myocardial infarction.—Ed.]

Brachial Neuralgia

Definition. Pain and paresthesias, sometimes with motor symptoms, in the neural distribution of cervicobrachial origin, and predominantly felt in the extremity, were termed "brachialgia." Such symptom-complexes presented in three main categories—brachial neuritis, cervical vertebral or disc disease, and disorders of the thoracic outlet—and were comprehensively reviewed.[3145]

Brachial Neuritis. Brachialgia presented as a localized neuritis of the shoulder girdle from lesions of the brachial plexus resulting from traumatic, infectious, or "idiopathic" causes. Some patients developed a "paralytic" form, with paralysis or atrophy of certain muscles of the shoulder girdle or extremity.[3137] In 82 patients with such "paralytic brachial neuritis" or "neuralgic amyotrophia," involving various nerves of the brachial plexus or combinations of them, the prognosis for recovery of power was good in most; the time required depended on the nerves affected.[3137] Among 28 patients with symptoms of unilateral brachial plexus neuritis was an instance of thyroid enlargement and hyperthyroidism. The symptoms were promptly relieved by antithyroid drugs.[1957] Brachialgia in some individuals was attributed to nervous tension, usually associated with "tension headaches" and "muscle spasm."[1605, 1929] Treatment of this type of brachialgia with phenylbutazone was effective in the majority of cases;[2052] in selected cases, introduction of procaine nerve blocks was effective.[994]

Vertebral Column Disease. Whiplash injuries of the cervical spine, particularly at the lower segments, produced brachialgia associated with pain in the shoulder. Originally ascribed to automobile accidents, these injuries were thought to be common occurrences in everyday life whenever the neck was snapped sharply by any direct or indirect force.[362] [It is of historical interest that a "whiplash" type of injury was involved in the first recorded instance of atlantoaxial subluxation, described by Sir Charles Bell before the Royal Society of London in 1822 (D.C.G.).—Ed.] The pain and its distribution along the extremity varied with the localization of the cervical injury.[247, 928, 2204] Pain in the upper extremity accompanied or alternated with pain referred to the scapular or precordial region. Sometimes pain along the vertebral border of the scapula or over the subdeltoid or the pectoral area was the only symptom of radicular irritation.[900]

Physical therapy, analgesics, and sedatives were regarded as useful therapeutic adjuncts, as were local injections of trigger points with procaine and hydrocortisone.[978] For some patients, sympathetic (middle cervical) blocks were advocated.[928, 1030]

Degenerative Arthritic Lesions of the Cervical Vertebrae [the pathology and roentgenography of which are reviewed in the Section on Osteoarthritis.—Ed.]. Vertebral osteophytosis was found to produce brachialgia.[255, 928, 1030, 2151] The sagittal diameter of the bony spinal canal was said to determine whether neural symptomatology or cord compression occurred.[3350] In 100 patients with a single disc protrusion established by operation, cervical discs compressing nerves from C_5 to C_8, individually or in combination, produced varieties of brachialgia, with characteristic sensory distribution and motor involvement, especially at the fingers.[3387] [This enlightening paper is worthy of study by those interested in the subject.—Ed.] Special radiologic technics for "symmetrical roentgenography of intervertebral foramina and of the cervical spine," for cervical osteoarthrosis or disc syndromes, and whiplash, producing brachialgia and other symptoms, were described.[983] Complete or segmental straightening (or reversal) of the lordotic

curve of the cervical spine was considered to be the most consistent characteristic feature, and very often the only abnormality found in whiplash injury of the neck.[362] [An x-ray report of "straightening" may be misleading. There may be no loss of mobility, and the changes observed on the roentgenogram may merely represent the way the head was held during roentgenography.—Ed.] X-rays might show maximal changes in patients with minimal or no symptoms, or, conversely, minimal changes in patients with severe symptoms.[1770]

Accepted methods of treatment with analgesics, cervical traction, and exercises for brachialgia arising from degenerative lesions of the cervical discs and vertebrae, with or without foraminal encroachment, were reëmphasized.[1014, 1030] Surgery for protruding discs with brachialgia and localizing neurologic signs was the subject of a favorable report.[3387]

Thoracic Outlet Syndrome. Brachialgia was a common finding among the neurovascular or thoracic outlet syndromes of the shoulder.[29, 2308, 2999] Two cases of subclavian aneurysm associated with cervical rib exhibited purely vascular symptoms. The release of emboli and a vasospastic element were thought to produce the symptoms; excision of the aneurysm and the cervical rib was recommended.[2245] Further attention was drawn to the possible serious results if the vascular symptoms in association with a thoracic outlet compressions syndrome were unrecognized. In a surgical unit in London, six patients with vascular insufficiency in an upper extremity due to cervical rib were admitted in 12 months.[2544]

The diagnosis of the thoracic outlet syndrome was assisted by certain maneuvers, but they were only "secondary aids" in diagnosis.[1562] Of 186 individuals without symptoms or pathology at the neck, supraclavicular area or extremity, 22% had a positive Adson test, 30% a positive hyperabduction test, and 9% a positive downward traction maneuver. Difficulties in identification of the various causes of thoracic outlet syndrome were due to the occurrence in the same individual of multiple abnormalities.[20] In a mass radiographic study of 67,716 people of all races in South Africa, cervical rib was found in 0.46%, somewhat more frequently in females than in males; it was more than one and one-half times as common on the right side; in 52.3% of cases it was unilateral, and in 47.7% it was bilateral.[2327]

In spite of the deëmphasis which the scalenus anticus syndrome has received for some time, a series of 230 patients with this syndrome was observed over an eight-year period; 76 were treated medically and 154 surgically.[2999] This syndrome was a late sequel of thoracoplasty in one case.[2308] Neurovascular symptoms in the hyperabduction syndrome, secondary to intermittent compression of the subclavian and axillary vessels and the lowermost cord of the brachial plexus, were discussed.[1938] The primary site of compression was "the point at which the vessels and nerves emerge from beneath the pectoralis minor tendon, with a secondary site of compression at the interval between the clavicle and the first rib"; five patients were subjected to pectoralis minor tenotomy and anterior scalenotomy, "with gratifying results in four."[1938] The individual frequently exhibiting these conditions, . . . "women who had drooping shoulders, drooping expressions and drooping spirits," warranted conservative therapy.[2373] Exercises readily followed at home to strengthen the elevators of the shoulder and to improve the posture of the neck, upper part of the back, and shoulders were effective in over 70% of the patients.[2373] [This program of management is now generally accepted, and should be used before surgical intervention.—Ed.]

Part III

Nonarticular Rheumatism

As in previous Reviews, this term included disorders characterized by musculoskeletal pain and stiffness of varying severity and distribution, unaccompanied by intra-articular disease. It was estimated that more than half of those seeking medical advice because of "rheumatic" symptoms presented with a condition in this group.[3232] [Of 552 new patients seen in the year 1954–1955 at the University of Michigan Hospital, 38 (6.5%) had complaints related to disorders with structures about joints (I.F.D.).—Ed.] A uniform diagnostic terminology was needed in this vague area, to indicate, insofar as possible, the nature and site of lesions. Sound classifications of the various components of nonarticular rheumatism were presented.[494, 556] [Much confusion is created by using the term "fibrositis" to apply to all forms of nonarticular rheumatism, including such definable, distinct entities as Dupuytren's contracture, bursitis and panniculitis. Preferably, the diagnosis of 'fibrositis" should be confined to the syndrome defined as such in this Review. Alternative terms to replace "fibrositis," not contributing to clarity, and based on unfounded concepts of pathogenesis, do not represent any progress in this respect.—Ed.]

Bursitis. A term frequently applied loosely to a number of entities capable of more exact diagnosis, *bursitis* was often a symptom of underlying disease and, as such, was not a proper diagnosis.[494] Bursae were susceptible to acute or chronic inflammation of specific or nonspecific etiology. Nonspecific bursitis, the most common form, was attributed variously to acute trauma with effusion, mild repetitive trauma, often occupational, or unusual strain. Commonly, there were no apparent causes. Chronic bursitis, with or without calcification, might follow incomplete resolution of acute bursitis or recurrent mild trauma.[68, 836, 2038, 2376, 2604]

Subacromial bursitis was usually secondary to underlying traumatic or degenerative changes in the supraspinatus tendon.[1896] Differentiation from meniscus cysts was considered to be important in two children with nonspecific bursitis adjacent to the medial meniscus of the knee.[1779] Relatively common and frequently misdiagnosed were acute calcific bursitis of the pisiform bursae at the wrist,[475] and calcific or nonspecific bursitis of peritrochanteric bursae about the hip. The latter required differentiation from other causes of low back, hip, and sciatic pain.[59, 162, 1859] The compensable disorder, colloquially termed "beat knee," an important cause of industrial disability among British coal miners, was defined as "a subcutaneous bursitis or cellulitis arising at or about the knee." Prompt diagnosis and simple treatment at the mine reduced disability appreciably.[855, 2543, 3237] Specific forms of bursitis were caused by pyogenic, tuberculous and sphilitic infections, and rheumatoid, degenerative and other forms of arthritis, gout and neoplasms. Bursitis was occasionally the first manifestation of R.A.[68, 836, 1648, 2038, 2604, 3120]

Treatment of nonspecific bursitis consisted of rest, immobilization, analgesics, including phenylbutazone, aspiration, and cold applications in the acute stage, and radiant heat, massage and exercises for subsiding acute or chronic bursitis. Infiltration with a local anesthetic and injection of hydrocortisone or related corticosteroids, repeated frequently as required, were recommended.[65, 68, 129, 162, 338, 556, 627, 673, 764, 836, 1521, 1648, 1896, 2038, 2267, 2376, 2447, 2604, 2678, 2705, 3125] Local injection of corticosteroids was unsatisfactory in many with chronic or adhesive

bursitis.[1790] Concentrated hydrocortisone, 150 to 200 mg. per cubic centimeter, was considered to be superior to the usual preparations.[634] [We are not convinced that doses of this magnitude are either necessary or desirable.—Ed.] Oral corticosteroids [2376] or steroid-buffered aspirin combinations [3105] were recommended by some, but gave only "fair" results in the experience of others.[3040] Ultrasonic therapy was beneficial,[431, 2004, 2267, 2391, 2626] though some thought its value not yet established.[203] X-ray therapy was beneficial for acute calcific bursitis.[764, 1859, 3125] Microwave diathermy,[2184] cobalt beam therapy [229] and iontophoresis using local anesthetic or vasodilating agents [2267] required further assessment. "Washing-out" of calcific deposits was advocated again.[764, 2376] Surgical excision of bursae [68, 2038] or calcific deposits [1815, 2678] was indicated only for a small minority who failed to respond to other measures. Unconfirmed and of questionable value were intramuscular adenosine-5-monophosphate,[3125] intravenous Priscoline,[1035] methyl salicylate ointment,[423] and oral hesperidin-methylene-carboxyl chalcone.[2358] Some patients with rheumatoid bursitis responded well to corticosteroid injections.[2604] Infective or suppurative bursitis was treated by rest, immobilization, local heat, surgical drainage, and appropriate antibiotics.[68, 836, 1648, 2038]

Tenosynovitis and Tendinitis. Nodular tendinitis and tenosynovitis were common manifestations of rheumatoid disease, and occasionally heralded its onset.[1548, 2319, 2429, 2645, 3120] Tuberculous tenosynovitis in the fingers, volar and dorsal wrist compartments, and tendon sheaths about the ankle was often difficult to distinguish from rheumatoid or nonspecific tenosynovitis. A combination of biopsy, culture, and guinea pig inoculation was more reliable for diagnosis than any single method.[557, 966, 3353] Nonspecific tenosynovitis, or "peritendinitis crepitans," distinct from stenosing tenosynovitis, affected the cellular, mucin-producing sheath lining and musculotendinous junctions of the flexor and extensor tendons of the wrist, forearm, fingers, Achilles tendon, and sheaths about the ankle.[557, 2354, 3332, 3353] Tenosynovitis of the wrist and dorsum of the foot resulted from self-inflicted trauma in a psychoneurotic patient.[181]

DeQuervain's Disease. Anomalies of the abductor pollicis longus and extensor pollicis brevis tendons and their sheath, "constitutional predisposition to connective tissue fibrosis," chronic repetitive trauma, and excessive use were factors of significance in pathogenesis. Palpable tender thickening over the radial styloid, pain on resisted abduction and extension of the thumb, and on passive abduction of the thumb, and Finkelstein's sign [see 11th and 12th Rheumatism Reviews (*1k, l*).—Ed.] were features of diagnostic significance. Snapping and locking did not occur.[86, 95, 557, 1842, 2560, 3003]

Stenosing Tenosynovitis. Stenosing tenosynovitis of the flexor sheaths of the thumb and fingers produced the clinical syndrome of "trigger finger." In infants, congenital constriction due to thickening of the sheath involved the flexor pollicis longus predominantly but not exclusively ("trigger thumb").[86, 95, 557, 1908, 2560, 2767, 3309] Rheumatoid tenosynovitis was a common cause of "trigger finger," [1842, 1908, 2645] but this phenomenon was attributed to coincidental nonspecific tenosynovitis.[2429] [In the experience of most of us, rheumatoid nodules frequently cause a "trigger finger."—Ed.] A rare stenosing tenosynovitis of both middle fingers in an infant patient was described.[1448] Chronic foot strain and pes valgo-planus were contributory factors in stenosing tenosynovitis about the foot and ankle. [1371, 2354, 2560]

Calcific Tendinitis (Periarthritis Calcarea). This was considered to be a specific entity due to degenerative changes, with subsequent calcium deposition in tendons, musculotendinous junctions, ligaments, fascia, articular capsules, annulus fibrosus of intervertebral discs, and other connective tissue structures. Most common in the tendons about the shoulder, particularly the supraspinatus, it also involved connective tissues about the elbow, wrist, fingers, hip, knee, ankle, and foot.[106, 1189] Calcific tendinitis about the wrist and hand, particularly in the flexor carpi ulnaris insertion at the pisiform, was frequently misdiagnosed.[2000, 3382] Acute calcific tendinitis of the flexor hallucis brevis insertion closely resembled acute gouty podagra in two patients.[344] Erosion of adjacent bone by calcific deposits occasionally required surgical curettage.[3294]

Carpal Tunnel Syndrome. This entity, caused by the compression of the median nerve beneath the volar carpal ligament, was frequently due to R.A. or tenosynovitis at the wrist, and at times constituted the presenting manifestation of that disease.[2097, 2115, 2389, 3153, 3224] It was also caused by gouty tophi,[3224] Leri's pleonosteosis,[2080] the shoulder-hand syndrome with sclerodactyly,[1655] and a wide variety of other lesions involving the wrist. Endocrine factors were suggested by its occurrence during pregnancy, at the menopause, and in association with acromegaly and myxedema.[1839, 2504, 3206] A "constitutional tendency to reactive fibrosis" [214] and intermittent vascular ooclusion at the pectoral level [485] were also implicated in its pathogenesis. The syndrome of acroparesthesia was attributed to this mechanism in the majority of cases.[768, 1104, 1383, 1960, 2504, 2985] "Cubital tunnel syndrome," designated a comparable disorder due to ulnar nerve compression beneath the aponeurotic origin of the flexor carpi ulnaris at the elbow, was manifested by "tardy ulnar palsy." [95, 960]

Tennis Elbow. This term, introduced by Bernhardt in 1896, was synonymous with disorders described as epicondylitis, radiohumeral bursitis, epicondylalgia, and golf elbow.[1190] It designated a painful and local tenderness and sometimes swelling and redness in the region of the lateral epicondyle of the humerus. It was attributed to a variety of lesions, including calcific tendinitis,[1190, 3159] degeneration or tears of the common tendinous origin of the forearm, wrist and finger extensors,[34] radiohumeral bursitis, and "nipping" of radiohumeral joint synovialis.[140] Proposed etiologic factors of doubtful validity were cervical nerve root lesions [1191] and "metabolic disorders due to dietary, nervous or hormonal disturbances." [2359]

Analgesics, rest, immobilization, strapping, splints, cold applications during acute stages and, later, local heat or diathermy were basic measures for the treatment of tenosynovitis and tendinitis.[3332] Local anesthetic infiltration and injections of hydrocortisone or related corticosteroids, repeated frequently as required, were advocated.[34, 129, 140, 556, 557, 627, 634, 673, 764, 1371, 1521, 1790, 1842, 1908, 2447, 2560, 2598, 2678, 2705, 3249, 3353, 3397] The value of ultrasonic therapy [203] and microwave diathermy [2184] remained to be established. Surgical division or excision of the affected sheath and freeing of enclosed tendons were usually necessary for stenosing tenosynovitis.[86, 95, 557, 764, 1448, 1842, 1908, 2319, 2354, 2560, 2598, 2678, 2705, 2767, 3003, 3309, 3353] Tenosynovitis at the ankle and foot required correction of foot strain and existing deformities.[1371, 3353] Oral corticosteroids with buffered aspirin [3105] and combined infrared and ultraviolet radiation [2711] were also recommended. [But only by the authors of these two reports.—Ed.] Some cases of calcific tendinitis responded favorably to x-ray therapy,[106, 344, 2000, 3125] to ultrasound,[431] and

to local procaine infiltration.[3382] Aspiration and washing out of calcific material were of doubtful value. Surgical excision of calcific deposits was indicated for the small number who did not respond to other measures.[1859, 2678, 3159] Large, persistent or disabling lesions of rheumatoid tenosynovitis required synovectomy, with repair of tendons if indicated.[2429, 2645, 3353] Most effective treatment of tuberculous tenosynovitis was surgical excision of the sheath, immobilization, and antituberculous drug therapy.[966] Tenosynovitis due to other infections was treated by surgical drainage and appropriate antibiotics.[557, 3353] Severe, persistent disability, thenar wasting, and weakness associated with the carpal tunnel syndrome were indications for surgical division of the transverse carpal ligament.[95, 214, 250, 277, 768, 1104, 1383, 1960, 2598, 2965, 3206] Excision of the volar carpal sheath if grossly hypertrophied[2389, 3153] and postoperative radiation were also recommended.[814] "Cubital tunnel" compression of the ulnar nerve was treated by division of the aponeurotic arch overlying the nerve constriction, and at times by transposition of the nerve.[95, 960, 2598]

Fasciitis and Fascial Fibromatosis. Combinations of Dupuytren's contracture, fibromatosis of the plantar fascia, dorsal knuckle pads and possibly Peyronie's disease suggested a common pathogenesis, "a diathesis leading to overgrowth, thickening and contracture of fascial tissues" in general.[70, 1760, 1806, 2069, 2839]

Dupuytren's Contracture. Hereditary influences were striking in Dupuytren's contracture which affected five brothers, their maternal uncle, and their maternal grandfather.[1760] The influence of trauma was both denied[652, 2069, 2194, 2195] and conceded a contributory role.[70, 1521, 2604] The concept was reiterated that partial, minute aponeurotic tears healed with scarring and fibrosis, proceeding at different stages in multiple sites in the palmar fascia.[2839] A controlled study of 15 patients with Dupuytren's contracture by means of the photoelectric plethysmograph revealed decreased vasomotor reactivity in unaffected as well as affected hands, in proportion to the degree of fascial involvement, and reversible to normal after excision of the diseased fascia.[2335] It was proposed that hyperplasia of the palmar aponeurosis, the early stage of Dupuytren's contracture, represented a "neurogenic tissue change or abortive shoulder-hand syndrome."[2581] [No convincing evidence was provided to support this theory. It remains to be established that the plantar fascial contracture in some patients with the shoulder-hand syndrome is identical with Dupuytren's contracture.—Ed.] Dupuytren's contracture in alcoholics with hepatic cirrhosis (66% of 57 patients) with significantly greater than in those without manifest liver dysfunction (27% of 55 patients), or nonalcoholics with no liver disease (12% of 53 subjects).[3352] Twenty per cent of 168 epileptics showed some degree of palmar fascial fibrosis; 12% had definite Dupuytren's contracture. There was no correlation with the type of epilepsy or its treatment.[100]

Pathologic studies of 61 specimens revealed fibrous tissue proliferation of fascia intimately associated with thick-walled vessels and increased capillary vascularity, undergoing maturation to form a relatively avascular scar; none of the features suggested an etiologic role of trauma, inflammation or neoplasm.[1826]

Radical aponeurectomy was advocated as the only effective treatment,[1660, 1806, 2069, 2839] but those with marked skin involvement, atrophy, and "dimpling" were treated first by subcutaneous "blind" fasciotomy, later by radical fasciectomy if necessary.[70, 652, 1087, 1826, 2886, 3247] Factors affecting operative results and post-

operative recurrence or extension were discussed.[541, 1205] Local hydrocortisone injection was considered to be of value.[673, 2447, 2705, 3397] Vitamin E, radiation therapy, and systemic corticosteroids produced no significant benefit.[70, 652, 1660, 2886, 3247] Minor, nondisabling degrees of involvement required no treatment.[2604] Idiopathic thickening of the tensor fasciae latae over the greater trochanter, a cause of "snapping hip syndrome," was successfully treated by subtotal division of the thickened tissue.[3361]

Painful Heels. Painful heels were caused by fasciitis at the attachment of the plantar fascia to the os calcis, occurring as a primary disorder or in association with rheumatoid or gonococcal arthritis [also rheumatoid spondylitis or Reiter's syndrome.—Ed.], foot strain, Achilles bursitis or tendinitis, and osteochondritis of the calcaneal apophysis in children.[890, 1088, 1372, 2767, 2948, 3120] Calcaneal spurs, per se, did not produce symptoms,[295] and their excision gave disappointing results.[1521] Treatment consisted of rest, hot fomentations or diathermy,[68, 2948] correction of foot strain, and modifications in shoe design.[295, 890, 1088, 1372, 1790, 2767, 2678] Local hydrocortisone injection was advocated,[68, 627, 1372, 1790, 2447, 2678] but its effects were comparable to those of saline,[295] and it was a "capricious and hazardous procedure."[1088] Persistent disability from Achilles bursitis required surgical reshaping of the posterior calcaneal surface.[2727, 2948]

Synovial Cysts. Baker's cysts resulted from cystic or myxomatous degeneration of juxta-articular connective tissue, or from semimembranous bursitis [or, most commonly, from herniation of articular synovial membrane.—Ed.]. The latter occurred spontaneously, particularly in children, or in association with mechanical derangements or various types of arthritis within the knee.[57, 68, 2767, 3120, 3405] An unusual synovial cyst of the hip presented problems in diagnosis of a painful inguinal mass.[501] Compression of the ulnar nerve and ulnar paralysis were caused by a ganglion-like pedunculated cyst of the elbow.[426] Synovial cysts in bone due to metaplasia or primitive connective tissue were capable of reversal to normal bone or malignant transformation to synovial sarcoma.[1423] A rare fibrocartilaginous cyst developed in the acromioclavicular intra-articular disc following trauma.[227] Injection of hyaluronidase[57, 3405] hydrocortisone or related steroids was recommended,[627, 2705] but was frequently unsatisfactory, or followed by recurrence.[2447, 2678] Surgical excision was advocated.[68, 2767]

Calcinosis. Most if not all cases of interstitial calcinosis were secondary to underlying "collagen disease"; clinical and biochemical evidence indicated an identical pathogenesis of universal and circumscript forms, the difference being one of severity only. [One of us (E.F.R.) disagrees. The differences are far more striking than the resemblances.—Ed.] Experimental studies implicating deficiency of "anti-stiffness factor" (stigmasterol) had no clinical application to date. Abnormal affinity of connective tissue ground substance for calcium was postulated.[1714, 3015] Massive "tumoral" soft tissue calcific deposits were described in two African natives.[2337] Devitalized tissue about a chronic varicose ulcer was the site of extensive calcinosis in a woman with widespread subcutaneous calcific deposits and Raynaud's phenomenon.[2540]

"Generalized articular calcinosis," an unusual syndrome of widespread calcification of articular capsules, articular cartilages, paravertebral tissues and the pubic symphysis, frequently asymptomatic but at times accompanied by local and constitutional symptoms, was described in two separate reports.[1685, 1939] Pellegrini-Stieda disease, para-articular calcification adjacent to the abductor tu-

bercle at the knee, was attributed to sprain of the medial collateral ligament with minor periosteal avulsion.[2283] Periarticular soft-tissue calcification and premature calcification of the aorta and main arteries were observed occasionally in Cushing's syndrome.[3223]

Corticotropin was advocated for calcinosis associated with "collagen disease,"[1714] but oral cortisone produced only a slight increase in calcium output, and no associated clinical or radiologic improvement was observed.[2417] Acetazolamide (Diamox) induced negative calcium balance and increased urinary calcium output in a patient with universal calcinosis. Sodium inositol hexophosphoric acid (Phytin) failed to increase fecal calcium, and decreased the calcium balance negatively achieved by Diamox when the two were given concurrently.[747]

Disorders of Muscle

Myositis Ossificans Progressiva. A connective tissue dysplasia was the underlying cause; the frequency of associated developmental anomalies, particularly microdactyly of thumbs and great toes, implied hereditary influences.[668, 2080] Transitional features of both progressive and circumscribed myositis ossificans in the same patient suggested a common etiology.[2834] [We consider these as generally distinct, unrelated entities.—Ed.] Progressive myositis ossificans was reported in two Asian Indians,[1124] and in a child with microdactyly, phalangeal synosteosis, and fused lateral masses of the cervical vertebrae.[2431] Treatment was symptomatic. ACTH or corticosteroids occasionally gave relief in the preossification stage of connective tissue hyperplasia. Investigation of the effects of chelating agents was recommended.

Circumscribed (Post-Traumatic) Myositis Ossificans. This condition was generally considered to be distinct from and unrelated to the progressive form. Soft tissue trauma, an important predisposing factor in the majority of cases, was absent in some. Features common to four patients with heterotopic bone in nontraumatized areas were prolonged immobilization, severe general illness, altered serum proteins, electrolyte and fluid balance, local edema, and impaired circulation in the affected areas.[1578] Thirty-three per cent of 236 patients with post-traumatic paraplegia developed soft tissue calcifications or ossifications between pelvis and knee level within six weeks to six months of paraplegia.[1919] Extensive ossification about the hip developed four months after the onset of paralytic poliomyelitis in a 12 year old girl.[1825] In its early stages, localized myositis ossificans occasionally resembled fibrosarcoma, or osteogenic or Ewing's sarcoma, clinically and pathologically.[10] [The important implications in differential diagnosis are obvious.—Ed.]

Epidemic Myositis (Bornholm Disease). The first epidemic definitely attributed to infection by Coxsackie virus, group B, type 2 (Dalldorf), occurred in Adelaide, Australia, in 1957.[840, 1644]

Polymyositis. The syndrome of polymyositis was recognized (1) as an independent entity of unknown etiology, (2) as dermatomyositis, if accompanied by skin lesions, (3) as a component of other "collagen diseases," and (4) in association with malignant neoplasms. Its resemblance to muscular dystrophies in children and to "menopausal muscular dystrophy" was often "striking."[2242] [Most observers now consider menopausal muscular dystrophy to be a form of polymyositis.—Ed.] Muscle biopsy and electrodiagnostic and electromyographic find-

ings were not always definite, but frequently provided useful diagnostic information.[2526, 3219] Electrocardiographic changes were nonspecific, and correlated poorly with cardiac pathology.[3199] Difficulties in differentiation of polymyositis from thyrotoxic myopathy, particularly in older patients, were stressed.[350] Polymyositis associated with acute thyroiditis in a patient with longstanding rheumatoid arthritis improved dramatically immediately after total thyroidectomy.[2768] Corticosteroids and vitamin E provided symptomatic relief during acute inflammatory stages, but were less effective if muscle degeneration predominated.[3219]

Diffuse suppurative streptococcal myositis ran an acute, fulminating, febrile course, terminating fatally with profound toxemia and circulatory collapse in four cases.[172] The importance of awareness of streptococcal infections of this type and of the need for prompt and vigorous treatment was emphasized. Acute, diffuse myositis was reported as a rare complication of varicella.[896] Spontaneous ischemic necrosis of leg muscles after exercise (march gangrene) was described in three patients. Immediate incision of the overlying fascia was recommended for preservation of maximal function.[286] "Psoas myositis" was frequently associated with lower abdominal pain mistakenly attributed to intra-abdominal inflammatory lesions.[279] [The nature and cause of this lesion and its role in symptom production were not entirely clear.—Ed.]

"Myalgia" and Myalgic Spots. Myalgia was attributed to "trigger areas" or "myalgic spots" in deep muscle or connective tissue. From these, noxious stimuli bombarded the central nervous system, setting up reflex cycles with stimulation of sensory, motor, and sympathetic pathways, resulting in pain, spasm and autonomic disturbances in "reference zones," at a distance from the "trigger points." Reference phenomena did not follow nerve or root patterns, but were anatomically constant and predictable for each "trigger point." Treatment included rest, immobilization, analgesics, sedation, physiotherapy, postural correction, and eradication of causative factors if possible. Many advocated "interruption of the reflex vicious cycle pain pathway" by spraying trigger areas with ethyl chloride or injecting them with local anesthetic, hydrocortisone or related corticosteroids, or by sympathetic blocks.[187, 231, 259, 337, 627, 764, 1135, 1284, 1285, 1291, 1929, 1930, 2209, 2495, 2598, 2678] Injection of trigger points with saline was as effective as local anesthetic in the experience of some.[2907] Other measures included psychotherapy, traction, manipulation, ultrasonic therapy,[2626] microwave diathermy,[2184] and methyl salicylate ointment.[423] Muscle pain induced by experimental "work" was attributed to tension stress in muscle fiber units, with swelling and edema of intramuscular connective tissue, and not to fiber tears or accumulated metabolic waste products.[121] [Many concepts of myalgia and treatment need further validation.—Ed.]

"Polymyalgia Rheumatica." A newly proposed syndrome of diffuse muscle pain, tenderness, and stiffness, observed in 12 patients, was described. Atypical R.A. or "collagen disease" was considered, but had not become diagnosable after observation for as long as three to four years. Weight loss, anemia, increased sedimentation rate and occasionally hyperglobulinemia were observed, but complete or partial recovery with little or no residual disability was the usual outcome after a course of a few months to a year or more.[83, 156]

"Stiff-man" Syndrome. This term was proposed for a previously undescribed disorder characterized by progressive, fluctuating muscular rigidity, with spasms at times approaching the severity of tetanus seizures, leading to rigid

deformities of the neck, trunk and limbs. Muscle biopsies from six patients showed no abnormality, though a myopathy was suggested by one autopsy report. Electromyographic patterns were those of prolonged contraction of normal muscle. A metabolic dysfunction was suggested by the presence in the urine of glucose or nonglucose-reducing substances, and by an abnormal inorganic phosphate response to a glucose load.[119, 420, 2169, 2296, 2437] [The 19 cases now reported suggest that this bizarre syndrome may be due to a metabolic disorder or possibly a myopathy of undetermined nature.—Ed.]

Fibrositis

Fibrositis was defined as a syndrome of soft tissue aching and stiffness, worse after inactivity, relieved by mild activity, heat and salicylates, and aggravated by overactivity, fatigue and certain climatic conditions. This syndrome occurred in "primary" form, or as a secondary manifestation of orthodox disorders, such as rheumatoid and other types of arthritis, and the "collagen diseases."[72, 603, 649, 2604, 2865, 2869, 3232] Terminology and concepts regarding its nature and diagnosis were confused. Its incidence was increasing steadily, according to estimates from one arthritis clinic.[72, 2869] [Without uniform diagnostic criteria for a disease which some think doesn't even exist, estimates of prevalence are difficult to assess.—Ed.]

Theories of eiology and pathogenesis described in previous Rheumatism Reviews were reiterated. Tension, anxiety, and emotional stress were important.[603, 2604, 3232] "Chronic fibrositis" was said to result from muscle atrophy due to sedentary living, poor conditioning, faulty posture, occupational overuse, mechanical defects or underlying musculoskeletal disease,[72, 2865, 2869] or was an expression of reference phenomena arising by reflex mechanisms from "myalgic" or "trigger spots." [See "Myalgic Spots," p. 190.—Ed.] Tears in the lumbodorsal fascia, with adhesions to the panniculus, and with a distribution of pain and tenderness following a spinal segmental pattern, were postulated as a cause of fibrositic back pain and sciatica.[781] In rare cases the syndrome was due to true myositis, possibly of virus etiology.[2994] [The etiology of "fibrositis" is unknown, the mode of symptom production is not understood, and there is wide variation in diagnostic criteria.—Ed.] Controlled histochemical studies demonstrated increased concentration of mucopolysaccharide, chlorides, extracellular water and mast cells in muscle which were the site of "fibrositic" symptoms secondary to intervertebral disc disease.[384]

Differentiation from rheumatoid or degenerative arthritis, disc lesions, "collagen diseases" and other organic disorders was often difficult. Yet the consistent character and distribution of symptoms, lack of bizarre description and reactions, influence of environmental rather than emotional factors, and relief by simple therapeutic measures distinguished fibrositis from psychogenic rheumatism.[603, 649, 2604, 2869, 2994]

Therapy required patience, sympathy, and explanation of the nature of the disorder. General measures included a sensible balance of rest, activity, and recreation; avoidance of fatigue and occupational stresses; use of analgesics, heat, massage, exercises, physical conditioning, and postural correction. Phenylbutazone, sedatives, and "tranquilizing" and "muscle relaxing" drugs were also recommended.[72, 231, 649, 1772, 2051, 2052, 2267, 2288, 2604, 2711, 2746, 2865, 2867, 2869, 2871, 3232] Elastic bandaging,[231, 2869] microwave diathermy,[1772, 2184] and iontophoresis with local anes-

thetics or vasodilators were also advocated.[2267] Ultrasonic therapy was used by some[2288, 2391, 2626] but required further assessment.[203] Injection of tender or "trigger" areas with local anesthetic,[649] hydrocortisone or other corticosteroids,[72, 2869, 2901, 3232] or saline,[2907] was of value. "Judicious use of steroids,"[2604] or prednisone and buffered aspirin,[3105] was both advocated by some and considered to be contraindicated by others. Hesperidin and ascorbic acid,[3232] or a hesperidin compound,[2358] was of unproved value.

Disorders of Fatty Tissue

Herniation of subfascial fat through defects in the lumbar fascia[649] was treated by hydrocortisone infiltration, with "good results" in nine patients.[2678] [The clinical significance of this entity is still unknown.—Ed.] Clinical features and treatment of the panniculitis seen most commonly in menopausal women and described in the Eleventh and Twelfth Rheumatism Reviews were restated.[556, 941, 3232]

The Rothman-Makai syndrome of nodular panniculitis, though histologically similar to Weber-Christian disease, exhibited smaller, deeper, more scattered nodules, resembling furuncles or erythema nodosum, which did not appear in crops or leave depressed scars, and were not associated with systemic febrile reaction.[2125] Arthralgia, transient arthritis or a chronic, progressive, symmetric polyarthritis, identical to R.A., was an accompanying joint manifestation.[943] [It is not certain, therefore, that this is a separate entity.—Ed.] Nodular panniculitis was reported as a sequel of dose reduction or cessation of prednisone therapy.[2868, 3063, 3179]

Unusual subcutaneous fat necrosis, with a lipophagic granulomatous giant cell reaction, fibrosis, and calcification was described.[39, 2002]

Weber-Christian Disease. Previously described theories of etiology of this condition remained unconfirmed. Trauma played a contributory role in localization of some lesions.[1174, 3043] In addition to involvement of the panniculus and perivisceral fat surrounding practically all viscera, lipogranulomatous lesions were observed in the small and large intestine, lung, lymph nodes, kidneys and bone marrow. Their complications included adrenal insufficiency due to adrenal infarction, necrotizing hemorrhagic bowel ulceration, small bowel obstruction, profound anemia, myocardial infarction and erosive-destructive lesions of subchondral bone.[1174, 2320, 2672, 2706, 2871] Marrow studies revealed marked abnormalities of plasma cells, myeloid giant cells and hyperplasia of megakaryocytes.[455] Unusual features included a prolonged course marked by a single pannicular nodule,[2419] widespread, severe vasculitis[2871] and liquefactive breakdown, ulcerations of overlying skin, sinus formation, and discharge of "pseudo-pus."[810, 1174] The second patient reported in the literature had had no relapse or sequelae of note 40 years after her original illness.[1706] The first case in an Asian Indian was described.[2178]

Treatment was supportive and nonspecific. Response to ACTH and corticosteroids was variable and inconsistent, but their use was considered to be "worthy of trial."[776, 2102, 2178, 2338, 2419, 2423, 2604] Antibiotics were usually without benefit,[810, 2419] but effected prompt clearing of lesions in one patient with associated suppurative upper respiratory infection.[2134] X-ray therapy was effective for lesions with liquefactive breakdown, skin ulceration, and sinus formation.[810]

Psychogenic Rheumatism

This diagnosis was applied to "that group of patients suffering from a psychoneurosis with fixation on the musculoskeletal system." Symptoms were usually multiple, vague, and bizarre. Discomfort was described in elaborate, imaginative terms. It was usually not relieved by heat or aspirin, or affected consistently by weather, activity or rest, but was more responsive to the patient's emotional state. Functional complaints referable to other systems were common. Grotesque posturing and gait, hypersensitivity of skin, muscle, and bony prominences, and a "touch-me-not" reaction, were frequently the only physical findings.[603] While rheumatic pain could have a purely psychogenic basis, it was commonly superimposed on organic musculoskeletal disorders, or perpetuated on a functional basis after the underlying disease had subsided.[2254] Pain, itself a state of mind, could be influenced or induced by other states of mind. However simple the underlying cause, it eventually resulted in bodily reactions, protective at first, but tending to set up spasm and contractures, in themselves additional causes of pain.[369] Pain was experienced as subconscious atonement for guilt, satisfaction of unfulfilled aggressive drives, or replacement for threatened or lost relationships. Its location frequently was determined by unconscious identification with a love object. No single psychiatric diagnostic category was applicable to all patients with this disorder.[911] It was proposed that emotional stress "translated as somatic muscle spasm resulted in pain as an expression of fatigue or vasomotor ischemia."[649] "Tension headache," a frequent accompaniment, was attributed to release of a hypothetic "stress substance" by the hypothalamus, which stimulated the branchial-derived cranial nerves and the pain-sensitive structures which they supplied.[1605] Patients with psychogenic rheumatism showed no absolute deficiency of circulating 17-hydroxycorticosteroids.[3225]

Of fundamental diagnostic importance was positive evidence of tension, anxiety or other abnormal psychologic reaction.[2254] Careful investigation was necessary to rule out organic disease, since manifestations of the latter could be subject to complex psychic distortion and elaboration, completely obscuring the organic origin.[649, 911, 1521]

In mild cases, explanation of the nature of symptoms, encouragement, and "tranquilizers" such as chlorpromazine, meprobamate, or Trilafon were recommended. Deep-seated, fixed psychic disorders required specialized psychiatric assessment and therapy.[231, 603, 1521, 2254, 2746]

Tumors of Synovial Tissue

Vim-Silverman needle biopsy was a simple, nontraumatic technic valuable in the diagnosis of synovial metaplasia, infections, tumors and other articular disease.[2611] [Synovial punch biopsy, using specially designed instruments, provides a useful, simple and safe means of early diagnosis not only of tumors but also of other disorders of synovial tissue, and its wider use is recommended. See Eleventh and Twelfth Reumatism Reviews.—Ed.]

Synovial Hemangioma. Cavernous, capillary and telangiectatic hemangiomas were classified anatomically as (a) juxta-articular (outside synovium), (b) intra-articular (lobular encapsulated masses attached to synovium by pedicles), and (c) intermediary (involving synovium diffusely, with extensions communicating with extra-articular tumor tissue, at times accompanied by heman-

gioma of the overlying skin). An intermediary hemangioma of the knee was not demonstrated by angiography because of thrombosis of communicating vessels between the tumor and main arteries and veins.[397] Complete excision was recommended.

Osteochondromatosis and Synovial Chondromatosis. Of unknown etiology, but generally considered to be benign neoplastic processes, these conditions represented variations in the same basic disorder arising from rests of precartilaginous tissue in transitional zones of synovium. Microscopically they could be traced through mesenchymal cells and fetal and adult cartilage to osteoid. Characteristically monarticular, they affected the knee, elbow, hip, ankle, wrist or shoulder in young adults, predominantly males. Few to hundreds of cartilaginous or osseous masses were embedded in thickened synovium, attached thereto by pedicles, or free within the joint cavity. Pneumarthrograms were a a diagnostic aid in some patients with chondromatosis. [Synovial punch biopsy has also been used to make this diagnosis.—Ed.] To only four cases of osteochondroma of the coronoid process of the mandible recorded in the literature, a fifth was added.[1875] Complete synovectomy gave good results in two patients,[1661] but postoperative recurrence was not uncommon, and malignant transformation was occasionally reported, justifying more radical surgery.[645] Solitary tendon sheath osteochondroma in the hand appeared in two female patients after trauma.[2230]

Pigmented Villonodular Synovitis. This term was applied to disorders previously designated as xanthogranulomas, xanthoma, giant cell tumors, and hemorrhagic villous synovitis, on the basis of a common pathogenesis and pathology. A similar lesion was occasionally secondary to degenerative arthritis or meniscus tears. Monarticular joint lesions involved mainly the lower limbs. Tendon sheath involvement was most common in the hands. Treatment required further evaluation.[397] Radiation therapy was recommended in selected cases,[1065] but synovectomy was preferred by most. Among four patients with involvement of the knee, one showed extension into the popliteal bursa.[375] Erosion of adjacent bone and, in some cases, loculated bone "cysts" were observed in nine patients with joint or tenosynovial lesions,[381] in one located completely extra-articularly adjacent to the knee,[2384] and in two with tendon sheath lesions in the fingers.[1912] Tendon sheath giant cell tumors or solitary xanthomas were distinguished from familial hypercholesterolemic xanthomatosis.[1991] A giant cell tendon sheath tumor of the finger presented as a huge, destructive, sloughing mass after 10 years' delay on the part of the patient in seeking medical care.[1007]

Synovial Sarcoma. This malignant tumor orginated from synovium of joints, bursae, tendon sheaths or fascial aponeuroses, was rarely intra-articular, and usually extended outward into soft tissues, with only focal attachments to its synovial origin. Occasionally it arose some distance from any synovial cavity, in soft tissues, or within bone as a so-called "adamantinoma." Although it was usually fatal within two years, instances of 20 and 28 years' survival despite repeated recurrences after local excisions were reported.[2050, 2665] A synovial sarcoma of the knee containing embedded peroneal and tibial nerves resulted in peroneal palsy and foot drop, and metastasized to pleura, lungs, diaphragm, and kidneys.[579] The anterior aspect of the neck [2050] and the sheath of the superior oblique muscle in the orbit [2910] were rare sites of involvement. Treatment remained unsatisfactory. Less drastic measures than amputation were recommended in selected cases.[1892]

Synovial Lipomas. Arborescent lipoma and lipoma simplex symmetricum were reported in tendon sheaths of the ankle and in the extensor carpi radialis, the latter resulting in tendon rupture at the wrist.[3012] An arborescent lipoma of both knees was associated with recurring yellowish translucent effusions and secondary osteoarthritis.[112]

Synovial Reticulohistiocytoma. Two patients had severe mutilating arthritis due to reticulohistiocytomas which involved synovium, joints, juxta-articular bone, skin, and lung.[2180]

Articular Disease Associated with Primary Bone Pathology

Clubbing of the Fingers and Hypertrophic Osteoarthropathy. The association of clubbing with intrathoracic pathology was noted by Hippocrates; today the concept has been broadened to include the role of diverse derangements associated with clubbing, and a pattern of relationship with hints as to mechanism begins to emerge. Systems involved and features of the osteoarthropathy which develops were described.[2758, 2796]

Idiopathic Osteoarthropathy. Three cases of a syndrome characterized by thickening and furrowing of the skin over the face, periostosis, and clubbing of the digits were encountered in England; diagnosis of acromegaly was ruled out. No pulmonary or other internal pathology related to the condition was established.[62] A single instance was reported in a man of 23.[428] [Facial alterations have also been reported in patients with "secondary" osteoarthropathy.—Ed.]

Acquired Hypertrophic Osteoarthropathy. The acquired form of hypertrophic osteoarthropathy may be considered in its relationship to the underlying disease.

Pulmonary. Clubbing of the digits was a clue to early diagnosis of intrathoracic malignancy.[1609, 2819] In contrast, a three-year x-ray study of 390 consecutive patients in a Veterans Administration hospital showed no single case of hypertrophic osteoarthropathy with pulmonary tuberculosis; in three patients where osteoarthropathy was uncovered incidentally, the final diagnoses were lung cancer in two and pyogenic abscess in one. It was stated that osteoarthropathy militates against a diagnosis of pulmonary tuberculosis.[2840] [Surgical advances and the introduction of antibiotics have made intrathoracic neoplasms the most important condition to be ruled out in the presence of hypertrophic osteoarthropathy. —Ed.]

Pulmonary neoplasms were the cause of hypertrophic osteoarthropathy in 20 of 22 patients with this syndrome,[1315] and in six additional cases.[1609, 2758] One patient with neurilemmoma of the diaphragm was described in whom the presenting feature was severe hypertrophic osteoarthropathy; this was the sixth case on record of primary neurogenic tumor of the diaphragm, and the second of neurilemmoma. Removal of the tumor led to rapid improvement in the osteoarthropathy; it was stressed that the high incidence of malignancy made early treatment imperative.[3123]

Cardiac. A rare instance of rhabdomyosarcoma of the heart associated with arthralgia, clubbing of the fingers, and periosteal proliferation was reported.[2357] A patient with a congenital heart defect (Eisenmenger's complex) and osteoarthropathy was described;[1609] two cases of congenital cyanotic heart disease with longstanding clubbing and hypertrophic osteoarthropathy were described. The

distinction between simple clubbing of the fingers and toes and hypertrophic osteoarthropathy was stressed.[3121]

Circulation. The role of the blood supply in the etiology of clubbing remained conjectural. Aneurysmal defects and vascular obstructions were reported to produce unilateral or localized clubbing often enough to implicate the circulation. Blood sampling by catheterization technics was done in a series of 33 patients with drumstick clubbing and a variety of types of intrathoracic pathology. The study demonstrated the presence of bronchopulmonary precapillary anastomoses in certain lung disorders, complicated by clubbing of the fingers.[701] In another series of 18 men with hypertrophic pulmonary osteoarthropathy, the circulation in the limbs was studied by venous occlusion plethysmography; there was generally a greater blood flow in those with osteoarthropathy than in the control group. After removal of the primary pulmonary lesion, there was a persistent reduction in flow in the forearm and calf.[1145] Obstruction of the left subclavian artery in a child resulted in clubbing of the fingers of the left hand; growth of the arm, hand, and fingers was not impaired.[3025] In a man of 28 who had a history of a gunshot wound of the chest, with resultant injury of the right axillary vein and pulmonary parenchyma, the fingers of the right hand were clubbed, and the entire extremity was hypertrophied. It was stated that an increase in peripheral blood flow beyond the tissue requirements was the major prerequisite for the development of clubbing.[2522]

Hepatic. A patient presenting congenital biliary atresia and skeletal abnormalities, including clubbing of the fingers and severe hypomineralization, was described.[1870] A Negro of 57 was found to have hepatomegaly (with amebic abscess), with alcoholism, diarrhea, and osteoarthropathy; he had had early clubbing of both fingers and toes.[580]

Gastrointestinal. Various metabolic abnormalities were considered as playing a role in the development of peripheral or skeletal responses to visceral malignancy.[3006] A case report was published of a woman of 64 with arthropathy associated with gastric carcinoma; since at the time of removal of the tumor the vagi were cut also, the prompt relief of joint pain could have been due to either intervention.[2351] In another case report, a man of 27 with regional enteritis involving the duodenum and with steatorrhea had clubbing of the fingers.[55] A boy of 10 was described as having anemia, diarrhea, weight loss, and clubbing of fingers and toes of four years' duration; x-ray showed periosteal new bone formation, especially on the ulna. The diagnosis of ulcerative colitis with hypertrophic osteoarthropathy was established.[1478]

Thyroid. Digital clubbing associated with exophthalmic ophthalmoplegia and thyrotoxicosis was reported in two men. The role of a pituitary gland abnormality in the production of clubbing was reviewed and discussed.[1043] In a Negro of 46, hypertrophic osteoarthropathy and pretibial myxedema developed following an induced remission of Graves' disease in response to the administration of I^{131}; similar changes were observed after treatment with thiouracil and subsequent thyroidectomy.[721, 2065]

Miscellaneous. Hypertrophic osteoarthropathy associated with lymphosarcoma was reported.[1208] The great variety of conditions which may underlie clubbing and hypertrophic osteoarthropathy was well represented by tabulation and analysis, with clinical data, methods of treatment, and results.[702, 1315, 2582] It was noted that removal of the chest lesion led to prompt cessation of the arthralgia

in 19 of 20 cases; vagus resection at the lung hilus had the same effect in each of three cases, and vagal block at the base of the skull relieved the symptoms in the extremities in five of seven cases.[1324] Vagotomy was followed by prompt relief of the symptoms and signs of osteoarthropathy in five patients.[1008] A well written and illustrated description of the anatomic changes and morphology of clubbing was reviewed.[258] A condition which required differentiation was epidermoid cyst of the bony phalanges.[1674]

Sarcoidosis. The great number of titles on this subject in the current literature bears witness to its widespread occurrence, the increased alertness in recognition, and a desire for a clearer understanding of it as a clinical entity. Surveys of history, definition, incidence, and general manifestations appeared.[56, 108, 720, 834, 972, 1083, 1525, 1720, 1923, 1969, 2128, 2250, 2683, 2814, 2850, 3109]

Clinical Lesions. Skin lesions in various diseases of the chest were described; these included the cutaneous manifestations of sarcoidosis.[2655] A patient exhibiting only cutaneous lesions and chance association of sarcoidosis with an unusual form of arthritis was reported.[2534] Muscular involvement as the only manifestation of the disease was reported;[53] random skeletal muscle biopsies in 42 patients with proved sarcoidosis yielded positive results in 23.[3207]

Sarcoidosis limited to the hands and fingers was reported in one patient.[1002] Bone changes in the extremities were described.[729, 2026, 2955] X-rays of a series of 81 patients showed characteristic lesions in the bones of the hands and feet in 17.2%; involvement of other bones was infrequent.[2955] Only nine of 120 patients exhibited such lesions, and routine radiographs were of little value in diagnosis.[2026]

The incidence of ocular involvement in sarcoidoisis was fairly high; a study of 23 patients listed the nature of the ocular lesion and the age incidence. Biopsy was necessary to confirm the diagnosis but was not possible when the lesion was within the eyeball.[691] Ocular sarcoidosis with fundus changes was reported in five patients from Denmark.[422] Of 100 cases of sarcoidosis reported from England, 28 showed ophthalmic manifestations; the effectiveness of local steroid therapy in controlling iridocyclitis was discussed.[28] A Negro girl of 11 with sarcoidosis, manifested by uveitis, pulmonary findings, and renal lithiasis was reported.[1642] Involvement of the lacrimal glands was described in two reports each dealing with one patient.[1269, 1585] Both patients exhibited keratoconjunctivitis sicca, and one of them[1269] a fully developed Sjögren's syndrome.

Bony involvement of the orbit with sarcoidosis in a girl of 16 and a Negro woman of 65 was described, with illustrations of the microscopic appearance of tissues.[289, 2872] Sarcoidosis of the maxillary antrum associated with widespread involvement of the right eye showed marked improvement three months after enucleation of the affected eye.[1913] Granulomatous lesions were found in the bone marrow of nine of 21 patients with sarcoidosis on whom aspiration was done; these were part of a series of 150 patients suffering from a variety of diseases.[2370]

Skeletal muscle biopsy was advocated as a diagnostic tool in suspected cases of sarcoidosis in the absence of skin or lymphatic node lesions; in four of five cases cited, the material obtained contained granulomata consistent with sarcoid.[2394]

Etiology and Pathogenesis. There was no knowledge of a specific agent which produced the characteristic tissue reaction in sarcoidosis. The relation-

ship to tuberculosis was a fading concept. The problem of etiology was approached by accumulating existing data in an attempt to perceive a pattern or to find a clue to a new approach.[2127, 2257, 2545, 2815, 2908] Concepts of epidemiology were proposed,[707, 1800, 2123] and the possible relationship between pine pollen and sarcoidosis was discussed.[706] Examples of a familial tendency to develop sarcoidosis were illustrated; one paper tabulated 23 such reports collected from the literature, and two families were described in detail.[3227] Sarcoidosis occurred simultaneously in a pair of 24 year old male identical twins,[43] and appeared in one of identical male twins, both of whom showed primary hyperparathyroidism.[2885] The role of trauma in producing sarcoidosis in scars of patients with pulmonary sarcoidosis was reported and discussed; 23 such "scar sarcoids" were tabulated.[1924]

Staining properties of sections of lymph nodes and skin from 72 cases of sarcoidosis were compared with those from other lesions, including malignancy, tuberculosis, and simple inflammation. Bodies of characteristic size and form reacted positively to the Schiff stain, and were found in 77% of the cases of sarcoidosis, but not in controls.[1528] Speculation as to the histogenesis of the epithelioid cell in the sarcoid lesion, and the role of endogenous phospholipid in its production, was tested experimentally; laboratory animals were immunized by repeated intraperitoneal injections of lipovitellin. Antigen injections were then found to produce the histiocytologic features of sarcoidosis.[2491] "Dusty vacuolation" and "glasslike" bodies in giant cells were described.[478] A case study suggesting a parallel between the development of lesions in miliary tuberculosis and in sarcoidosis was reported, and views on the clinical pathogenesis of sarcoidosis were discussed.[2127] A report on bacterial residues in sarcoid lesions suggested that they were previously tuberculous.[2257]

Immunology and Tissue Sensitivity. Experiments testing the possibility of an antigen-antibody reaction as the basic mechanism in the etiology of sarcoidosis failed to establish such a reaction. The serum gamma globulin level in patients with sarcoidosis was directly related to the activity of the disease.[1022]

Study of the Kveim reaction continued. It appeared to be positive in only some of the patients with clinically proved sarcoidosis. An impressive series of 234 patients who did not have sarcoidosis included only two who reacted positively. The test was described, and its possible mechanisms were discussed.[2249, 2251, 2501] Further studies in sarcoidosis and tuberculosis using the Kveim technic were reported,[1523, 1755, 2502] and a comparison with the lepromin reaction, the Mitsuda test, was made.[1756] The lack of a delayed skin reaction to tuberculin and other antigens in sarcoidosis, and the use of tuberculin in oil, or of tuberculin plus cortisone, suggested that there was a low sensitivity to tuberculin in the skin of patients with sarcoidosis; the conjecture that sarcoidosis might arise from tuberculous infection was revived.[561, 562, 1558, 2257] Latex fixation tests were positive in six of 61 patients with disseminated sarcoidosis, none of whom had R.A.; the significance of this and relationships with other conditions were considered.[1781]

Treatment. Although treatment with ACTH and/or steroid hormones brought about some definite signs of improvement, these were probably temporary. The aim of treatment was to maintain the patient until a stage of natural remission occurred.[3084] [Corticotropin and the adrenal steroids currently enjoy the most popularity in treatment.—Ed.] Cortisone was recommended for serious disability such as (a) eye lesions, (b) advanced pulmonary involvement, (c) hypercalcemia, (d) hypersplenism, (e) cardiac involvement,[2481] (f) parotid involve-

ment, (g) renal involvement, and (h) erythema nodosum.[1524] Results of therapy with ACTH and steroids were reported.[54, 1418, 1556, 2648, 2918, 3257] Hypercalcemia with renal impairment responded well to steroid therapy, according to most reports.[1152, 2095, 2393] One patient showed improvement with antituberculous drugs after only partial improvement with ACTH.[543]

Gaucher's Disease. The association of skeletal changes and symptoms with an enlarged liver and spleen was noted. A diagnosis of Gaucher's disease could often be suspected after the inspection of the roentgenograms of the bones.[2884] Of three patients with biliary cirrhosis, hypercholesterolemia, and bone lesions, two had articular lesions; it was concluded that mechanical weakening and replacement of subchondral bone by foam cells were important in the genesis of the articular lesions.[92]

Osteochondritis. An excellent discussion of definitions, etiologic and clinical considerations, and classification helped to clarify some of the confusion from the continued use of eponyms and diverse terminology.[2035] Legg-Calvé-Perthes' disease was defined as osteochondritis in some reports, and as osteochondrosis in others.[1022, 1308, 2485, 2638] Unilateral Legg-Calvé-Perthes' disease occurred almost simultaneously in two brothers, aged five and seven;[445] dizygotic male twins developed coxa plana within two months of each other during their fourth year.[761] The same lesion occurred simultaneously at five years of age in another pair of twin boys.[2893] The pathologic changes observed in biopsy specimens in two cases consisted of necrosis of the femoral head and disruption of the epiphysial plate, with resultant irregular endochondral ossification.[2420] The almost constant increase in the so-called "tear-shaped phenomenon" was helpful in the diagnosis. In two series of 10 patients each there was no evidence of thyroid dysfunction.[213, 539]

In the knee, loose bodies were found in the anterior recess of the lateral meniscotibial joint space, and in the sheath of the popliteus tendon.[2963] Traumatic osteochondritis of the knee joint was described in 55 patients, and emphasis was placed on the importance of early correction of injuries in preventing the formation of osteochondritis.[654] "The only aspect of Osgood-Schlatter disease which was not controversial [was] its diagnosis."[607] It was suggested that this condition resulted from a dislocation of appositional structures within the tibial tubercle complex, that this dislocation was not preceded by underlying disease, and that it could most easily be ascribed to trauma.[607] These views were supported by studies of seven[1840] and 19 specimens,[2472] and x-ray examinations of 75 patients with a clinical diagnosis of Osgood-Schlatter disease.[1501]

Two patients with involvement of the caput humeri were reported.[1835] Epicondylitis of the humerus (128 instances in 119 patients) was the subject of a report; local injections of hydrocortisone and surgical treatment were described and the results tabulated.[2426] Bilateral osteochondritis of the middle cuneiform bone developed in a five year old boy six months after an injury.[2882] The middle sesamoid of the great toe was described in three patients, and two similar cases were cited from the literature.[123] Tarsal navicular osteochondritis (Köhler's disease) was reported in 55 patients; there was the characteristic increase in density of the bony shadow, with reduction in size, flattening, and fragmentation with repair.[669] The clinical and radiologic features of osteochondritis ischiopubica were described.[1473]

Various features of treatment methods and results were reported.[934, 1639, 2476,

[3367] Of 52 patients with Legg-Calvé-Perthes' disease, one third developed good, one third fair, and one third poor femoral heads.[933] Remarkable results followed treatment of four patients with tibial tubercle epiphysitis by local injection of cortisone derivatives.[2980] Operative treatment was performed with excellent results on 14 patients with osteochondritis of the tibial tubercle; the criteria for surgical intervention were (1) repeated attacks of severe pain, tenderness, disability, and deformity, (2) failure of conservative treatment, and (3) sufficient age (high-school age) and height to justify the excision of the tubercle.[3092]

Osteochondritis Dissecans. It was stated that this was not a clinical entity in itself, but probably a type of osteochondrosis, the etiology of which was not understood.[2035, 3110] Incidence in the Army service age group was reported as 427 (2.3%) from a total of 18,405 men. Distribution of joints affected was tabulated, and the literature reviewed; case reports were included.[1996] The etiology was either traumatic or embolic; of significance were the findings in caisson disease, in which the ends of certain long bones showed subchondral aseptic necrosis, with devitalization of the articular cartilages, which became irregular and rough.[2425] Osteochondritis dissecans associated with dwarfism was reported in three instances;[3296] it was also associated with tibia vara in a father, two sons, and a daughter.[3110] Congenital indifference to pain was described in a report of six cases, each with skeletal manifestations, including one instance of osteochondritis or aseptic necrosis.[2660] Osteochondritis dissecans of the hip treated by various methods was reported in a series of eight patients.[1271]

Involvement of the knee was reported in 10 patients,[1804] and in 55 patients with follow-up.[1885] A detached piece of bone reunited after immobilization of the knee in a 14 year old boy.[262] Spontaneous healing in children was seen in six cases of osteochondritis of the knee, and was said to be the rule rather than the exception; treatment might shorten the course.[2725] A girl of seven developed osteochondritis dissecans of the knee four years after a solitary eosinophilic granuloma of the skull.[182] Osteochondritis dissecans developed in the ankle after injury, with symptoms simulating fracture, but no fracture had occurred.[476] The second phalanx of the middle finger of one hand was the site of involvement in a boy of 13; clinical and radiologic healing occurred after nine months.[1529]

The course of healing, with or without treatment, was discussed, and operative procedures were described and illustrated.[2850] The value of conservative management in the child and growing adolescent was illustrated by a boy of eight years.[3136] Surgery of the patella was described, and the rare involvement of this structure by osteochondritis dissecans was noted.[3122]

Dysplasia epiphysalis punctata, a rare congenital disorder of infancy, affecting particularly cartilage, muscles, joint capsules, and the eyes, was the subject of a case report; radiologic and histologic features were described.[1632]

Osteitis Pubis. This was described as an inflammatory disease of the anterior pelvic girdle which developed during or after pregnancy, trauma or pelvic surgery. Clinical features as they occurred in 13 female patients, one of whom was biopsied, were described; symptomatic therapy was advised.[3336] Treatment of osteitis pubis with local infiltration of hydrocortisone acetate was reported in five cases; in four of them, initial treatment with ACTH was followed by relapse.[180] Arthritis of the hip complicating osteitis pubis after retropubic prostatectomy was described; antibiotics were ineffective; natural healing followed, with absorption of the femoral head, leaving a painless joint with good function.[587]

In another report, four instances of osteomyelitis of the pubic junction were cited; it followed extensive pelvic surgery in one case, suprapubic prostatectomy in two cases, and the repair of urethrocele through abdominal route in one case. Excision and drainage of the abscess, along with appropriate antibiotics, relieved the symptoms. It was emphasized that osteitis pubis required careful scrutiny, and that appropriate measures should be taken to recognize infection in the bones on either side of the symphysis pubis.[1659]

Miscellaneous Conditions. Urticaria pigmentosa of the adult type, and of long standing, was presented with illustration of x-ray findings and histologic sections of bone lesions suggesting mast-cell granuloma of bone.[2932] X-rays of 52 patients with urticaria pigmentosa detected generalized or localized bone changes in 19; the findings indicated that the tissue mast cell had affinity for the bone marrow, causing osteoporosis and osteosclerosis.[2642] The difficulty of diagnosis was illustrated by two cases of boys of nine and 17 months in whom the first skin biopsy failed to demonstrate mast cells; the relation of the mast cell to histamine and heparin metabolism was discussed.[394]

An epidemic of smallpox in Nigeria in 1957 provided 15 examples of osteomyelitis variolosa in children; the clinical and radiologic features of the disorder were presented.[602]

Wilson's disease (hepatolenticular degeneration), associated with an excessive absorption of copper from the intestinal tract, and the likelihood of copper deposition in the brain and liver, was reported in 20 patients, 14 of whom were shown to have a variety of osseous lesions; the possibility that there was a disturbance of phosphate metabolism, or that the abnormal copper metabolism caused skeletal abnormalities, was considered.[979]

Two patients with ischial epiphysiolysis were reported and no treatment was advised; the end result was usually satisfactory with conservative treatment.[2935]

Congenital Defects Involving Joints

Ehlers-Danlos Syndrome. Faulty organization of collagen networks was the basic defect; changes in elastic fibers were secondary.[2077, 2078, 2081] Hypothalamic-pituitary factors were implicated in some.[1886] Onset as a bleeding diathesis was reported.[1549] Capillary fragility was due to perivascular collagen deficiency, not to primary defects in vessel walls or coagulation factors.[1056] Previously undescribed epidermal cysts received comment.[1505] The typical syndrome was reported in a brother and a sister.[2641] Cutaneous hyperelasticity and joint hypermobility were common among 500 unselected persons.[905] "Arthrochalasis multiplex congenita," articular hypermobility and flaccidity without dermatologic or vascular changes, was distinguished from true Ehlers-Danlos syndrome.[1369]

Morquio-Brailsford Syndrome. Clinical and radiologic features were reviewed.[1732] Hereditary transmission was unlikely, though familial incidence was not uncommon.[2080]

Arthrogryposis Multiplex Congenita. Fetal agenesis or abiotrophy of the cerebrum [897] or anterior horn cells [109, 1627] was postulated as the basic cause, with muscle changes as secondary effects. Possibly analogous was the association of amyotrophic lateral sclerosis with congenital articular deformities.[1784] Other evidence implicated a primary muscle abiotrophy without central nervous system

involvement.[153] Satisfactory rehabilitation was attained by many.[2096] Association with esophageal stenosis, infantile cortical hyperostosis,[584] and webbing of the neck[1003] was reported. Hereditary transmission was doubtful.[2080]

Gargoylism. Liver glycogen was replaced by complex mucopolysaccharides, including a heparin-like polysaccharide not found in the patient's brain or in normal tissues.[269] [Recent studies indicate that the abnormal macromolecular storage material in nervous tissue is relatively insoluble mucopolysaccharide-phospholipid; that in other tissues, a freely diffusible mucopolysaccharide.—Ed.] Interference with calcium accretion was attributed to mucopolysaccharide storage material at sites of normal calcium deposition.[400] Chondroitin sulphate-B and heparin sulfate were present in the urine of four patients with this syndrome, heparin sulfate only in the urine of a fifth. The type of polysaccharide had no apparent relation to clinical severity or postulated mode of inheritance.[2119] Gargoylism in American Negroes[921, 1137] and in Asian Indians[1249, 1711] was reported for the first time, as was its association with neurofibromatosis in the same family.[3407] Additional case reports[2031, 2646] and general reviews[1732, 3408] were recorded.

Pseudohypoparathyroidism. In this syndrome, end-organ recalcitrance to normal circulating parathormone was manifested by a dyschondroplasia, soft-tissue calcinosis, tetany, hypocalcemia, and hyperphosphatemia.[457, 1101] Pseudo-pseudohypoparathyroidism designated a syndrome of a similar dyschondroplasia and calcinosis, but not accompanied by the clinical or biochemical features of hypoparathyroidism. The fourth reported case was described.[2092]

Marfan's Syndrome. Incomplete syndromes, which outnumbered classic cases, could at times be clarified by genetic study of the family. Resemblance of the lesions to those of lathyrism suggested a similar biochemical fault.[2821] "Formes frustes," mainly ocular and pedal abnormalities, affected several relatives of a typical Marfan patient.[1742] Another Marfan kinship was notable for skeletal and cardiovascular defects, sparing the eye.[3331]

Osteogenesis Imperfecta. Broad expressivity of an autosomal dominant mutant gene resulted in varied clinical syndromes overlapping Marfan's and Ehler-Danlos syndromes.[2079, 2081] Enzyme deficiencies were implicated in both osteogenesis imperfecta and chondrodystrophies.[1146]

Rare Hereditary and Congenital Musculoskeletal Disorders. The Klippel-Feil syndrome of developmental anomalies in the cervical spine was associated in one patient with spastic paraplegia, thought to result from malformation in the spinal cord, sparing cerebellar and sensory pathways.[2827] Other reports dealt with dyschondroplasia,[1732, 2080] punctate epiphysial dysplasia.[2392, 2770] multiple epiphysial dysplasia,[1045, 2780] progressive hereditary diaphysial dysplasia,[2953] arthro-onychodysplasia,[393, 1944] Maffucci's syndrome,[226] chondro-ectodermal dysplasia,[2167] Leri's pleonosteosis,[2080] and megalodactylia.[542] [The number of recognized rare hereditary and congenital defects of joints is increasing. Available space allows listing of only the names of these entities. The possibility that their biochemical study may yield fundamental information concerning connective tissue metabolism seems excellent.—Ed.]

Structure and Function of Articular Tissues

Basic Structure of Connective Tissue

The status of research in connective tissue was comprehensively summarized.[807, 808, 1254, 1255, 1256, 1535, 2864, 3133, 3235] Connective tissue, consisting of fibrillar ele-

ments and ground substance, including cells and mucoprotein material, was vital to storage and transport of water, electrolytes, and many metabolites vital to the economy of the body. This tissue was also a "target organ" in most of the rheumatic diseases.

Collagen and Other Fibrous Components. *Collagen.* Recent research was conveniently divided into considerations of structure, chemical composition, genesis, and alterations due to age or to insult of physical, chemical or enzymatic nature.

Structure. Convenient names for the various units of the collagen fiber were suggested.[3235] The gross collagen fiber could be split into smaller units, called "fibrils," and seen with the standard light microscope. These in turn were composed of smaller units, "microfibrils," seen by electronmicroscopy; some of the latter were as large as 2,000 Å. The splitting of microfibrils yielded "filaments," which in turn were further divided into "primary fibrils." The basic units, or "building blocks," 2,000 to 3,000 Å long and less than 50 Å wide, were called "tropocollagen" [1257] or "procollagen." [2323]

Electronmicroscopy revealed a banded appearance in microfibrils; at least six bands were identified for each 640 Å period, and seemed to consist of granular material.[3234] X-ray diffraction, light scattering, viscosity measurements, and electronmicroscopy [314, 1203, 2104, 3112] were employed in ascertaining the nature of the collagen molecule; it was rod-shaped, and had a width of 13 to 15 Å. Its molecular weight was estimated as 345,000.[314] Collagen fibrils were arranged in the form of a helix, and a unit was comprised of three such fibrils.[2459, 2489] These units appeared by x-ray diffraction to be formed in a crystal lattice.[200, 2458]

Chemistry. The aminoacid content of collagen was analyzed.[845, 1536] Fish collagen resembled that of mammalian sources, except for a slightly lower content of proline and hydroxyproline, and higher values for serine and threonine.[845] Collagen constituted approximately one third of total body protein, and in man consisted of 13% hydroxyproline. Chains of polypeptides comprising the basic unit of collagen contained glycine-proline-hydroxyproline units.[3274] The chemically reactive groups in collagen appeared to be the amino, the carboxyl, the guanidine, and the hydroxyl groups.[348]

Genesis. Formation of collagen fibrils with typical 640 Å banding within 72 hours was observed by utilizing cultures of osteoblasts.[1540] This material was rich in hydroxyproline, and chemically corresponded closely to collagen. Before fibril formation, the osteoblasts contained cytoplasmic granules which stained using the periodic acid Schiff (PAS) method. Fibroblasts from tendons of fowl embryos showed similar cytoplasmic components.[1541] It was thought that the intercellular ground substance also contributed to fibrillogenesis.[2468, 3066] In chick embryo tissue, the forming collagen fibers were in direct continuity with the fibroblast.[3233]

Special technics for stimulating collagen production or promoting tissue growth in culture were described, using carrageenin,[859, 1537, 2841] sponge implantation,[330, 355, 3061] a collagen-gel medium,[894] and other special media.[1638] Rat tendon cells were capable of synthesizing proteins, and the pattern of aminoacid incorporation was studied.[1338] Fibroblasts of mice showed an active uptake of $S^{35}O_4$ during fibrillogenesis.[1158] Cell growth and fiber formation in the chick lung were unhampered by lack of ascorbic acid in culture experiments,[3349] in contrast to in vivo observations in guinea pigs.[66, 1212, 1213] Studies with labeled glycine

suggested that the terminal glycine residue on collagen units may be replaced at a rate different from that of the other glycine residues.[1112]

Elastin. The concept that elastin fibers were evolved by obscure alterations in collagen continued to be attractive. Electronmicroscope studies[1649, 1650, 1651] showed that moth-eaten fibers (MEF) were produced by the action of collagenase upon human or ox collagen, and appeared as large, dense, segmented bundles with irregular holes. A material called "metacollagen" was prepared from pure collagen from rat tails,[150] and possessed many but not all of the features of elastin. Following thermohydral contraction in water at 67° C., the collagen fiber lost a mucopolysaccharide component and a soluble protein material. The remaining "metacollagen" then, in common with elastin, possessed properties of elasticity in water, birefringence increasing in lipoid solvents, ability to be digested by elastase, failure to show swelling in dilute organic acids, and an electronmicroscopic pattern similar to that of elastin.[150]

Elastin was also reconstituted from soluble material from ox ligamentum nuchae.[3356] Collagen incubated with phthalate buffer produced a residue richer in valine than parent collagen, thereby showing a chemical change in the direction of elastin.[1304] [These studies of the relationship of elastin to collagen are intriguing and stimulating. However, the concept of collagen as a predecessor of elastin remains unproved.—Ed.] The action of pancreatic enzymes on elastin revealed several different enzymes.[149] The existence of enzyme components of elastase (E_1 and E_2) was proposed;[1306] one of these (E_1) reacted with the mucoid fraction of the elastin fiber. This elastomucase fraction of elastase was further characterized.[2680]

Reticulin. The nature of reticulin, the silver-straining fiber network of base-

TABLE 3

Composition of the Mucopolysaccharides

Mucopolysaccharide	Repeating Disaccharide	Components		
		Hexosamine	Uronic Acid	Other
Hyaluronic Acid	Hyalobiuronic Acid	Glucosamine	Glucuronic Acid	—
Chondroitin Sulfate—A	Chondrosin	Galactosamine	Glucuronic Acid	Sulfate
Chondroitin Sulfate—B	Disaccharide (analogous to Chondrosin)	Galactosamine	Iduronic Acid plus Glucuronic Acid	Sulfate
Chondroitin Sulfate—C	Chondrosin	Galactosamine	Glucuronic Acid	Sulfate
Chondroitin	Chondrosin	Galactosamine	—	—
Keratosulfate	—	Glucosamine	—	Galactose Sulfate
Heparin	—	Glucosamine	Glucuronic Acid	Sulfate
Heparin Sulfate and other Heparin-like Substances	Unknown			Some Without Sulfate

References 808, 1085, 1449, 2110, 2120.

TABLE 4
Tissue Sources of Mucopolysaccharides

	Hyaluronic Acid	Chondroitin			Chondroitin	Keratosulfate	Heparin
		A	B	C			
Aorta	*	*	*	*			
Bone (Calf or Ox)	*	*		*		*	
Cartilage		*		*			
Cock's Comb	*						
Electric Organ of Eel				*			
Cornea		*			*	*	
Fibroblasts	*			*			
Heart Valves			*	*			
Ligamentum Nuchae			*				
Mast Cells	?						*
Neoplasms	*	*		*			
Skin	*		*				
Synovial Fluid	*						
Tendon			*	*			
Umbilical Cord	*	*		*			
Vitreous Humor	*						

References 1085, 2110, 2120.

ment membrane, was still obscure, but some of the dispute and confusion was resolved.[2546] Similar fibers were observed in newly developing connective tissue areas not related to basement membrane. These fibers differed from basement membrane by differential solubility on extraction with citrate solutions,[1534] and by studies of antigenicity.[2712, 2713]

An additional "new" connective tissue fibril, with banding periodicity of 270 Å and interperoids of 20 Å, was described in frog tissue.[2326] Another new fiber, the "oxytalan fiber" occurred particularly in ligaments, tendons, and connective tissue sheaths.[1084]

Ground Substance and Mucoprotein. The ground substance was that portion of connective tissue which existed between the cellular and the fibrillar portions. Protein and polysaccharide components, soluble forms of collagen and other as yet unidentified components were present in this amorphous matrix. Current knowledge of ground substance was reviewed.[331, 808, 912, 1425, 2193, 2864] Mucopolysaccharides of ground substance included hyaluronic acid, the chondroitin sulfates A, B, and C, chondroitin, and keratosulfate. These are listed in table 3. Sources of these mucopolysaccharides are listed in table 4. A method for total mucopolysaccharide determination was described.[334]

Hyaluronic Acid. Hyaluronic acid (H.A.), originally isolated from vitreous humor in 1935,[2120] was present in connective tissue in general, and was isolated from placenta, umbilical cord, certain microörganisms, synovial fluid, certain tumors, and cock's comb. H.A. was increased in connective tissue of scorbutic pigs.[2553] Human synovial membrane in tissue culture produced H.A.[1388] Chemically, H.A. was composed of highly polymerized hydrophilic molecules existing as a strongly hydrated gel or in a highly viscous solution.[293] Acid hydrolysis of enzymatic digests of hyaluronic acid [2120] yielded a glucouronidoglucosamine which was called hyalobiuronic acid; its elaborate chemical configuration was described [1449, 2118, 2120] as a repeating unit of β-d-glucosylpyruronic acid-3-0 glucosamine. Other studies of the physiochemical properties of H.A. were reported.[146, 303, 305, 2193]

H.A., with a molecular weight of 58,000, was isolated from human sera. It was found to be susceptible to degradation by pigment from *Pseudomona* organisms [763] and by extracts of *Flavobacterium* heparinum.[1758] It failed to serve as an antigen in rabbits.[2449]

Cysts associated with Heberden's nodes contained H.A.[1533] The degree of polymerization of H.A. in R.A. was reduced, as indicated by viscosity measurements,[889] but this polymerization was increased after the administration of hydrocortisone.[889]

A test for minute amounts of H.A. utilizing toluidine blue was described.[308] The H.A. in the presence of the dye produced a precipitate differing in color from precipitates caused by other mucopolysaccharides.

Hyaluronidase and Inhibitors. Hyaluronidase, the enzyme capable of depolymerizing hyaluronic acid by hydrolysis of the β-hexosamidic bond, was usually obtained from bacterial (streptococcus) or testicular sources, but *Pseudomonas aeruginosa* was also capable of producing this enzyme, which seemed to be associated with the pigment present in cultures of this organism.[1572] Most assays for hyaluronidase activity depended upon the observation of the spread of a dye or hemoglobin in the tissue studied. Applying solutions of bacterial hyaluronidase and testicular hyaluronidase to the inner surface of rabbit skin and subsequently comparing the spread of subcutaneously injected hemoglobin solution in these pretreated areas indicated that bacterial hyaluronidase possessed markedly greater penetrating properties in connective tissue than did the testicular enzyme.[606]

Another technic utilizing measurements of increase in size of vesicles containing the test substance in the isolated connective tissue of mice was described. [2703] Hyaluronidase activity was assayed in concentrations as low as 0.01 turbidity reducing units per milliliter by observing the decapsulation of streptococci exposed to the test solutions.[2039] A new micromethod was also described.[1154]

Heparin and chondroitin sulfate were competitive inhibitors of hyaluronidase. [1482] [Other heparin-like substances are also inhibitory.—Ed.] Saliva contained a hyaluronidase inhibitor,[2620] and a hyaluronidase accelerator was present in serum. [3100] Hyaluronidase was used to increase the rate of flow of fluid during hypodermocylysis, and to reduce pain in joint and muscle sprains.[3172]

Mucopolysaccharides and Mucoproteins. Except for hyaluronic acid, chondroitin, and certain heparin-like mucopolysaccharides (as yet incompletely described), the remaining known mucopolysaccharides were sulfated compounds. The chondroitin sulfates A, B, and C were described in detail.[294, 1694, 1922, 1981, 2120]

Sources of chondroitin sulfate A (C.S.A.) included aorta, calf bone, hyaline cartilage, corneal tissue, certain neoplasms, and umbilical cord. The structure of C.S.A. was that of a repeating disaccharide unit called chondrosin, made up of glucuronic acid and galactosamine joined by a β-1,3-glucuronidic bond. It was proposed [2120] that the disaccharide units were joined by a β-1,4-hexosaminidic bond analogous to that of hyaluronic acid. The molecular weight of chondroitin sulfate from beef cartilage (nasal septum) was measured at 40,000 to 50,000.[3245]

Chondroitin sulfate B (C.S.B.) differed from C.S.A. and chondroitin sulfate C (C.S.C.) in optical rotation measurements. C.S.B. was isolated from aorta, heart valves, ligamentum nuchae, skin, and tendon. Like C.S.A., its molecular structure consisted of a repeating disaccharide unit analogous to but not identical with chondrosin. Two different disaccharide units in C.S.B. were suggested: one contained galactosamine with iduronic acid, and the uronide of the other appeared to be glucuronic acid.[1450, 1458] Chondroitin sulfate C (C.S.C.) has been isolated from aorta, bone, cartilage, the electric organ of the eel, fibroblasts, heart valves, neoplasms, tendon, and umbilical cord sources. It was similar in structure to C.S.A., consisting of repeated units of chondrosin (galactosamine and glucuronic acid). The optical rotation, however, differed. It was suggested that the sulfate radical was located at a different point from that in C.S.A.[2028, 2120]

Heparin, a polymer of a glucosamine-glucuronic acid sulfate-containing unit, was found in mast cells.[1085] In addition to its function as an anticoagulant, heparin was involved in fat transport, served as an inhibitor of hyaluronidase, and had an antihistaminic effect.[1085]

Biosynthesis of the mucopolysaccharide was observed in tissue culture.[1261] Human fetal skin or bone produced hyaluronic acid and a chondroitin sulfate. Synovial cells in vitro were also capable of mucopolysaccharide production.[517] Uridine nucleotides were a possible source of the uronic acid portion of mucopolysaccharides.[808, 2864] The amide nitrogen of glutamine was the source of the amino group in glucosamine.[808] Glucosamine enhanced the incorporation of S^{35} labeled sulfate in chondroitin sulfate of cartilage.[2572] Galactosamine had a similar but less potent effect. Glutamine also enhanced S^{35} uptake in nucleus pulposus.[2571] A factor in liver homogenate had a similar enhancing effect on the uptake of S^{35} in cartilage slices.[2573] The rate of synthesis of mucopolysaccharides in rabbit skin was studied with C^{14} and S^{35}.[2697] Glucosamine and the N-acetyl moiety of the hyaluronic acid turned over at the same rate, whereas chondroitin sulfate was metabolized at a slower rate. Cortisone inhibited this metabolic process.[2696]

A variety of means of identifying mucopolysaccharides were reported. Gentian violet staining for heparin and polysaccharide sulfate esters was described.[1328] The use of a triple stain, with the Feulgen reaction, periodic acid-Schiff stain, and napthol yellow S, was helpful in differentiating nuclei (blue), polysaccharides (red), and proteins (yellow).[1436] Thionine metachromasia,[749] Schiff's reaction, and Hale's test [1575] were useful in the study of tissue mucopolysaccharide content. Cetyl pyridinium chloride-aqueous formaldehyde and 5-aminoacridine hydrochloride were used as fixatives for tissue to be studied for mucopolysaccharides.[3314] A turbimetric measurement, utilizing cetyltrimethylammonium bromide, proved to be a useful quantitative method for measurement of isolated acid mucopolysaccharides.[771]

The lack of antigenicity of chondroitin sulfate obtained from human cartilage

and injected into rabbits was demonstrated.[2448] Methionine added to the diet of protein-deficient rats increased production of mucopolysaccharides.[3144] Mucopolysaccharides were found in the serum of normal[329] and of diseased[341, 717] human beings. The increased levels in the sera of rheumatic disease patients were the result of smaller molecules produced as a result of the disease state, thereby enhancing the transport through the vascular walls. Chondroitin sulfate was isolated from normal human plasma[2695] and urine.[770] The severity of disease seemed to be related to the level of α-mucoproteins, according to one study,[717] whereas growth processes seemed to be reflected in an increase in α-2-mucoprotein levels.

Mast Cells. Study of mast cells was hampered by their variability in size (8 to 20 μ), shape (spherical, spindle or stellate), and tissue distribution. These cells, described in 1877 by Ehrlich, were still characterized by the metachromic staining of their cytoplasmic granules. Several reviews summarized the current state of investigation of these interesting connective tissue components.[219, 1085, 1424, 2330, 2878, 3286] The granules of mast cells were uniform in size (0.3 μ) and globular in shape. Other cells, such as fibroblasts, were capable of ingesting these granules, and thereby resembled mast cells in staining properties.[1424, 2855] The fine structure of mast cells was studied by electronmicroscopy of sectioned mast cells obtained from the peritoneal fluid of rats and Syrian hamsters.[2854]

Tissue mast cells (differentiated from the basophils of the peripheral blood by the lack of water solubility of their granules) were observed in normal bone marrow[1584] and throughout the circulatory system, including all layers of the human aorta (especially the ascending portion) and the pulmonary artery.[2412] Smaller arteries contained mast cells in the outer layers. All veins had mast cells in the adventitia, but only the vena cava possessed intimal mast cells. These cells were observed in the epicardium and interstitial tissue of the heart. They were also present in rat myocardium, the number seemingly reduced with age.[630] They were also present in the pericardium, pleura, and liver capsules of cattle and horses,[3255] the liver of rats,[3072] rat peritoneum,[2066] esophageal lining of cats,[1576] gingival tissue,[3044] the endosteal surface of bones of calcium-deficient rats,[3147, 3148] and the human umbilical cord.[2192]

Mast cells responded to a great variety of stimuli. Exposure to cold caused an increase in the number of mast cells in rat mesentery and skin;[1844] a similar increase occurred after calciferol intoxication.[1143] Other forms of stimulation resulted in mast cell disruption and release of granules. Considerable interest has been shown in the response to compound 48/80 (a condensation product of formaldehyde and p-methoxy-phenethyl-methylamine). Intraperitoneal injections of 48/80 in rats were associated with a disruption and degranulation of mast cells.[1277] Protamine and turpentine oil produced the same effect. Perfusion studies of rat hind quarters revealed that the 48/80 effect resulted in liberation of both histamine and serotonin.[251] Increased plasma histamine was observed in healthy dogs and in dogs with mastocytomas after administration of 48/80, the response being greater in the latter group.[1829] Perfusion studies with cat paws showed histamine release after 48/80 stimulation.[1452] Various metal salts also inhibited the action of 48/80 on mast cells.[1453] In contrast to 48/80, reserpine caused the release of serotonin, but not histamine, from mast cells of rats, without causing cell disruption.[251] The systemic administration of ACTH and cortisone and the local application of hydrocortisone to the cheek pouch in

hamsters were found to result in degranulation of mast cells.[3253] Similar changes were observed in human tissue after cortisone administration.[297] ACTH in rats resulted in similar mast cell degranulation.[3178] No effect of testosterone could be observed during studies of mast cells in cock's comb.[3039] Antigen-antibody experiments in mice[500] and rats[3264] resulted in mast cell alterations after the antigenic stimulus was applied.[1662, 3254]

Heparin was produced in the mast cell, and represented about 3% of mast cell net weight.[2330] Careful studies of mast cell distribution and tissue concentration of heparin in rats and rabbits, however, showed little correlation between mast cell prevalence and heparin content.[2005] Other studies have shown a much better correlation.[1085] Hyaluronic acid production also occurred in these mast cells.[1085, 1432] [Evidence for this is still controversial.—Ed.]

Serotonin production also occurred in mast cells,[252, 1085, 3284] and accounted for approximately 0.1% of their net weight.[2330] Serotonin was not found in mast cells of all species;[508] its concentration was high in mouse mast cell tumors, but it was not present in dog mast cells.[2833] [Serotonin has not been demonstrated in human mast cells.—Ed.] Serotonin was found to be closely associated with inflammatory reactions, and was capable of producing increased capillary permeability in low concentrations.[2349, 2922] Release of serotonin was responsible for symptoms of anaphylactoid reactions,[3285] since its release from mast cells occurred in such experimental situations. However, in another study of anaphylaxis in rats,[2211] although both serotonin and histamine were released, antihistamines protected the animals from shock. Serotonin also caused release of water-binding mucopolysaccharides from mast cells.[116]

Histamine was also a prominent constituent of mast cells, accounting for approximately 1% of their net weight.[2330] Release of histamine by "liberators" occurred without permanent cellular damage,[2330] and occurred to a differing extent when the same stimulus was applied to different species.[2346] Histamine release from mast cells was inhibited by antihistaminic substances.[2330] Degranulation of mast cells following histamine administration was demonstrated in hamsters.[113, 3252] The process of histamine liberation was due to a lecithinase.[2536, 3152]

A transplantable mastocytoma of a mouse contained abnormally great quantities of histamine, heparin, and serotonin.[1090] The appearance of mast cells in lesions of urticaria pigmentosa was documented.[394, 1921, 2275, 2642, 2932, 3399]

Amyloid. Analysis of amyloid tissue compared with control material showed an increase in nonhexosamine protein-bound hexose from amyloid kidneys and spleens.[1822] At least one fraction of amyloid substance bore a closer relationship to serum glycoproteins than to the mucopolysaccharides of ground substance origin. In patients dying from pulmonary tuberculosis, amyloid-bearing livers and kidneys examined before and after trypsin and pepsin digestion revealed that sulfated polysaccharide was present in the amyloid deposits, and that the mucopolysaccharide was probably of the chondroitin-sulfuric acid type.[3339] In tissue from patients with secondary amyloidosis, it was also possible to show, by Coon's fluorescent antibody technic, that the amyloid deposits contained considerable quantities of gamma globulin.[3166] [We agree this does not prove that an antigen-antibody reaction is involved in deposition of amyloid.—Ed.]

Amyloidosis was reversibly produced in rabbits by the repeated subcutaneous injection of sodium ribonucleate.[2532] During the period of amyloid deposition, there was a marked rise in levels of serum beta-globulins, and of one globulin

component which, by electrophoresis, was not a normal serum constituent. It was suggested that a beta-globulin might be directly involved in the formation of amyloid deposits. [Perhaps the beta-globulin is a by-product.—Ed.]

Polysaccharide-containing globules were found in reticuloendothelial cells of the liver, kidney, and blood vessels in close proximity to deposits of amyloid in mice, guinea pigs, and rabbits.[3070, 3071] Electronmicroscopic studies of secondary amyloidosis showed localization of the amyloid material in the glomerular capillary basement membrane.[1111]

Synovial Tissues and Synovial Fluid

Anatomy. *Synovial tissue* occupied the inner aspect of the joint capsule and varied greatly in thickness. It was a loose areolar or fibrous and sometimes fatty tissue containing small arterioles, capillaries and venules. The lining of flat or cuboidal cells was one to four or more cells thick. The surface of the synovialis was villous. Terminal nerve endings in joint capsule deep to but not in the synovial membrane indicated little innervation of the synovialis.[1490, 2836, 2984, 2985] A method of determining the area of articular surface was described.[2862, 2863]

Synovial fluid continued to provide a ready substrate for clinical investigations. Studies of normal human fluid[167, 1311, 2396, 2402, 2587] and bovine fluid[306, 307, 1952, 2258] were reported. Normal fluid was clear, usually contained less than 100 leukocytes per cubic millimeter, had a high relative viscosity, and contained a sugar concentration approximating that of the serum.[2587] Viscosity was determined by the concentration and degree of polymerization of hyaluronic acid,[333] and in ox synovial fluid depended upon a protein-hyaluronic acid complex.[306] Normal synovial fluid had an average intrinsic viscosity of 70 units, as compared with an average of 38 units in cases of R.A. Digestion of the protein portion of the complex with papain produced marked reduction in viscosity. A rolling-ball viscometer was introduced[165] which permitted determination of viscosity on small (two drops of fluid) sample amounts. The protein fractions of the mucin clot of ox synovial fluid consisted of albumin identical by electrophresis with serum albumin and a γ globulin.[1952] Electrophoresis of whole normal synovial fluid indicated that, in most cases, albumin, $\alpha 1$, $\alpha 2$, β and γ globulin could be identified.[2402]

In R.A. and similar disease states, the proteins of synovial fluid were[2701, 2702] qualitatively identical to those of the serum by electrophoretic, ultracentrifugal, immunochemical, solubility, and ion-binding measurements.[2701, 2702] In R.A., the potassium in synovial fluid varied with the degree of activity of the disease;[1979] synovial fluid hyaluronate was decreased[1314] and sialic acid was increased.[2395]

Physiology of Synovialis. The metabolic activity of synovialis was studied in vitro.[777, 778, 3080] Normal synovialis had a very low oxidative metabolism, although glucose utilization and glycolysis occurred at moderate rates. In rheumatoid arthritis, these indices of metabolic activity were of much greater magnitude. Synovialis was capable of synthesizing in vitro[516, 3384, 3385] hyaluronic acid utilizing glucose labeled with C^{14}. Cortisone, hydrocortisone, and some other adrenocorticosteroids inhibited synovial metabolic activity in vitro.

Studies with I^{131}-labeled albumin[1776, 1777] showed that synovialis was permeable to albumin, with a disappearance rate more rapid in R.A. patients than in normal individuals.[24] Permeability to sodium, measured by Na^{24} clearance,[1340]

was decreased in normal joints by obliteration of the blood flow, and increased by the application of deep heat. Clearance rate was increased in the presence of inflammation but decreased by light, nonweight-bearing exercise.[1342] Hydrocortisone caused a decrease in sodium concentration of synovial fluid of R.A. patients.[3383]

Articular blood vessels were controlled by sympathetic vasconstrictor fibers, and were sensitive to adrenalin and noradrenaline.[596, 597] Local [595] or remote [2378] heating of the body caused vasodilatation and increased intra-articular temperature. Fibrinolytic activity was reduced or absent in synovial tissue [122] and fluid.[32]

Physiology of Cartilage

Studies of cartilage, its constituents, and its metabolism have been concerned with the active metabolic unit, the chondrocyte, with the fibrillar components, and with the amorphous ground substance. Electronmicroscopic studies have been performed which show the anatomic arrangements of cartilage fibrils.[477]

Intense activity of chondrocytes in newborn albino rats was revealed by autoradiography of their humeri soon after C^{14}-labeled sodium carbonate was administered.[1245] However, specimens obtained 24 hours after administration of the labeled compound showed less activity in the chondrocyte and more intense reaction in the cartilage matrix, especially in areas near chondrocytes. Some labeling of the chondroitin sulfate also occurred, and it was suggested that the C^{14} was utilized in the synthesis of the cartilage matrix (especially collagen).[1245]

Younger chondrocytes near the articular cortex showed a greater metabolic activity, as measured by accumulation of extracellular chloride, than did older chrondrocytes nearer the cartilage surface.[403] Labeled sulfate [87, 709] was first metabolized by the chondrocyte, but the uptake was impeded or destroyed by mechanisms toxic to the cell.[87, 709]

Several enzyme systems have been demonstrated in cartilage homogenates, including intracellular dehydrogenase activity,[1016] hexosamine,[511] and alkaline phosphatase.[1405] Adenosine-3-phosphate-5-phosphosulfate was formed and converted into chondroitin sulfate in particle-free extracts of chick embryo cartilage.[715] Glutamine increased the rate of formation of chondroitin sulfate.[2570] In rats the lathyrus factor impeded formation of mucopolysaccharides;[2443] and removal of gonads, adrenals, or both glands, stimulated cartilage growth (except in gonadectomized males),[430] again showing hormonal effects upon cartilage growth. [See also Section on Experimental Arthritis.—Ed.]

Studies of chondroitin sulfate, present in the amorphous ground substance and also in close association with collagen, by light-scattering and ultracentrifugal technics,[243, 244, 245] suggested that the chondroitin sulfate-protein complex existed in cartilage as a polydisperse system of coils. A molecular weight of 50,000 was calculated for chondroitrin sulfate.[2029] Chondroitin sulfate content of cartilage decreased with age.[2996] Chondroitinase from *Proteus vulgaris* caused degradation of cartilage chondroitin sulfate to form uronic acid, sulfate, and hexosamine.[788] Cartilage also contained a noncollagenous protein.[2258, 2349]

Development of Articular Structure

In the embryology of the human hand,[1231] the joint cavities first appeared when the fetus reached 30 to 50 mm. in length after nine to 11 weeks [earlier in

more central joints (fifth week).—Ed.] All joints were represented after the fetus reached 65 mm. in length. Although capillaries were found at an earlier stage (30 mm.) in the loose tissue around bone ends, synovial tissue appeared later (at approximately 45 mm.). Synovial membrane could be identified at a still later stage (60 to 110 mm.), and nerve fibers appeared at this same time in the joint areas. Ligaments and capsules appeared earlier (13 to 30 mm.). The importance of motion of the joint in promoting its development was demonstrated in vitro with knees of chick embryos.[1882]

Joint and Muscle Pain

Anatomic dissections in man demonstrated that the nerve supply of tendons came not only from the attached muscle but also from communicating branches of cutaneous nerves or of nerves from deeper structures.[2983, 2986] Termination of these nerves was of three types: Ruffini-like organs, small encapsulated corpuscles, and/or free endings.

The pathogenesis of pain in muscle and elsewhere was discussed generally[101, 1096] but remained obscure, although several pertinent factors were identified by utilizing the denuded base of a skin blister as a testing model.[105, 1652, 1653] Several substances often associated with injury or inflammation were capable of causing pain, including 5-hydroxytryptamine (serotonin), histamine, and a polypeptide substance called "PPS" (pain-producing substance) by Keele.[1653] This latter material, found in plasma, synovial fluid, and blister fluid, was labile. Its activity appeared a few minutes after the fluid was removed from the body, yet decreased in potency after an hour. Trypsin was capable of actuating PPS.

Joint Motion

Problems of mechanics and lubrication of joint motion were compared to similar problems of machinery.[166] Maintenance of a lubrication "wedge" between two rotating surfaces of differing radii was important in the preservation of joint surfaces as well as of axes. Synovial fluid, with its high viscosity at rest, was an ideal lubricant for joint surfaces; its function as a lubricant was discussed.[304] The mechanics of knee motion,[2861] and of other joints,[1962, 1963, 1964] including those in cadavers,[749] were reported. Although most systems of measuring joint motion in angles made the assumption of a stable fulcrum, the actual center of rotation varied with joint position.

Careful measurements of joint range of motion were important in following response to therapy.[3317] Protractor-like devices for such measurements were inaccurate, and a triangular method was suggested[3317] whereby a measurement was made along the extremity on each side of the joint between points equidistant from the fulcrum (the joint). As the joint was flexed, these point approximated. The actual angle of flexion was a function of the distance measured. An "improved" goniometer was described that consisted of a small disk surrounded by a circular column of fluid containing an air bubble.[2687] When it was strapped to a moving part, a changing angle representing the range of motion of the joint was indicated between the position of the bubble and the long axis of the moving part.

Bone Physiology

Structure. Electronmicroscopy of bone and cartilage matrix revealed pertinent information regarding physiology of bone.[2561, 2562] Fibrils which make up bone matrix in the newborn infant were 500 Å in diameter and associated closely with osteoblasts. The cross striations of these fibrils resembled those of collagen. The fibril diameter was greater in specimens from older individuals, 600 to 800 Å being observed in middle age, and up to 1,500 Å in senile adult fibrils. The cement space between fibrils was narrower in bone matrix than in cartilage.

Crystals appeared early in close relationship to fibrils,[2776] and in a random pattern. In older bone, the long axis of the crystals paralleled that of the fibril axis. Bone crystals were shown to contain calcium, sodium, magnesium, potassium, phosphate, chloride, and the fluoride ions, in addition to trace amounts of other components. The precise chemical arrangement of bone mineral was not yet clear, but approximated hydroxyapatite. The crystals varied in size from less than 25 to 1,500 Å in length, and from 25 to 75 Å in width.[2427] A tremendous surface area was thus presented for interaction with body fluids. A "hydration shell" of water covered the crystal surface and could not be removed by mechanical means such as centrifugation. Knowledge of the ultrastructure of bone was reviewed.[2084]

Mineral Constituents of Bone. Up to 46% of the total body sodium was present in crystalline bone.[2273] The induction of severe acidosis in rats revealed the participation of bone mineral sodium in the mobile body pool.[1876] [The mobility of bone mineral sodium is an important practical consideration in the computation of sodium lack in patients who are subjects for replacement therapy. Consideration of extracellular fluid volume alone is not adequate.—Ed.]

Other minerals had important functions in bone development. Manganese lack in the diet of swine[2247] was associated with shortened bones and areas of osseous rarefaction resembling osteitis fibrosa, filled with dense fibrous tissue. Sulfur, as represented by S^{35}, appeared in bone in high concentration at sites of active bone growth[1695] and throughout bone in a labile form. Presumably this was distributed over the crystal surface, since it could be removed by decalcification processes, unlike the nonlabile S^{35} found in areas of active bone growth.

Since advances in physical science have resulted in alterations in the "normal" constituents of bone in some geographic areas, it has become important to consider the metabolism of elements such as strontium. Sr^{89} entered bone mineral at an uptake rate of 1.08 times that of calcium.[1857] There was a selective removal process, however, since Sr^{89} loss from bone mineral was 1.2 times that of calcium in in vitro studies of cultured embryonic chick bones. Sr^{85} was also excreted at a faster rate than was calcium.[192] [Obviously, these studies cannot be translated directly to human physiology. Preferential absorption of calcium vs. strontium in the gastrointestinal tract and selective excretion of strontium vs. calcium by the human kidney complicate the in vivo studies.—Ed.]

The metabolism of Ba^{140} in man paralleled that of calcium, suggesting its use as an indicator of skeletal metabolism in human beings.[193] Radium in human bone appeared irregularly in small, patchy areas in compact as well as cancellous bone.[1936]

Bone Formation and Destruction. The mechanical basis of bone formation was reviewed;[2714] it was again suggested that trabecular patterns form along the

lines of pressure in a functional bone. By in vivo dog bone grafts, bone formation was stimulated by bone necrosis.[130] An "osteogenic inductor factor" extractable from bone paste was reported.[2210] Osteogenesis was examined in vitro, using chick embryo epiphysial cartilage.[2748, 2749] Calcification was observed between 50 and 80 days after explanation, whereas the peak of alkaline phosphatase activity was reached from 25 to 40 days from the start of the culture. Acid phosphatase activity was low but rose slightly after from 15 to 40 days. Calcification also was observed in vitro in calf skin, tendon, and demineralized cortical bone.[3004]

Alkaline phosphatase was found in high concentration in the cytoplasm of osteoblasts from chick embryo frontal bone in in vitro studies.[1404] This activity was not found in fibroblasts except when these cells were associated with degenerative changes.

Blood taken from the spongiosa of the dog showed a striking output of citrate when the animal was stimulated by intravenous parathormone;[2259] presumably the citrate from the bone carried complexed calcium with it, resulting in loss of bony calcium.

Research Approaches. Administration of amino-acetonitrile to rats produced bony lesions resembling excessive callus formation;[2734] the rats were sensitized to the action of amino-acetonitrile by concomitant administration of the dye substances alizarin and kernechtrot.[2733] Juxtaposed mounting of a stained histologic section of bone and its radiograph facilitated the study of cartilage calcification.[318] Low-angle scatter x-ray technics have continued to be employed in the investigation of bone material.[467, 468] A calcium-infusion test was useful in differentiating between osteomalacia and osteoporosis;[985, 2284] patients with osteomalacia tended to retain intravenously administered calcium; normal controls and osteoporotic patients excreted the administered dose more rapidly.

Hormonal and Other Drug Influences Upon Connective Tissue

The various elements of connective tissue were responsive to a great variety of hormonal and other influences.[114, 115, 806, 1723, 2509, 2889]

Hydrocortisone and Cortisone Effects. At the cellular level, both hydrocortisone and cortisone were again shown to be capable of inhibiting the growth of fibroblasts. In the inhibition of mouse fibroblast growth in vitro, hydrocortisone was more potent than cortisone.[1458] In cells from mice, chickens, and rabbits the concentration of cortisone (0.1 to 0.01 mg./ml.) could be adjusted to inhibit adult but not embryonic fibroblasts.[1113] Hydrocortisone inhibited cultured cells of human origin from malignant and nonmalignant sources.[1741] Fibroblasts exposed to anti-inflammatory corticosteroids became rounded, and the hormone was concentrated at the cell surface.[811] The effect of corticosteroids upon inflammation, immunity, and allergy at the tissue level was reviewed.[1120] Artificially produced granulomas remained a reliable method of testing the anti-inflammatory activity of steroids.[1416, 2379, 2550] Cortisone and ACTH inhibited anaphylaxis in guinea pigs,[1583] and cortisone suppressed edema in the mouse paw injected with silver nitrate solution.[640] The anti-inflammatory activity of cortisone upon the granuloma pouch in rats was found to be independent of the presence of the thyroid gland in rats.[320] Growth hormone, however, inhibited this action of cortisone upon foreign-body granulation tissue.[2036] Pulverized autoclaved car-

tilage overcame cortisone inhibition of healing in a granuloma pouch.[1832] The 9-α-fluoro-analogs had enhanced potency in the suppression of granulation tissue.[2822]

When applied topically, C^{14}-labeled hydrocortisone penetrated the skin and localized about small blood vessels, and disappeared after 16 hours.[2710] In the rat, large doses of cortisone caused atrophy of the epidermis.[2226] Softening and atrophy of keloids were also produced in man by local injections of hydrocortisone.[117] [There seems to be little reason to doubt or to emphasize further the inhibitory action of hydrocortisone on fibroblasts.—Ed.]

Growth of chick cartilage was inhibited following cortisone administration;[1493, 2890] growth hormone antagonized this inhibition.[2887] Hydrocortisone given to hypophysectomized rats inhibited the normal distribution within cartilage of administered para-amino-salicylic acid, and growth hormone could overcome this inhibition.[754]

The effect of cortisone on bone growth was also inhibitory. In the rabbit the administration of cortisone was followed by bone resorption and cessation of bone growth; normal status was regained when the steroid was discontinued.[2995, 2996] Cortisone also inhibited regeneration of injured salamander limbs.[1988] In children, growth was inhibited mildly by cortisone administration, but was resumed after cortisone was discontinued. [R.A. itself may retard growth.—Ed.] In children with hypopituitarism, however, severe growth inhibition occurred with low steroid doses.[296]

Cortisone administration was associated with an increase in hydroxyproline concentration in mouse muscle.[1054] A decrease in hexosamine content of rat skin following cortisone administration was observed.[2888] A direct effect of ACTH—decreased capillary permeability in inflammatory lesions in dogs—was reported.[2110]

Desoxycorticosterone (DOC). DOC inhibited inflammatory exudate in the granuloma pouches of rats.[2549] Low doses (500 μg. daily) of DOC in chickens had no effect on proliferating cartilage.[1494]

Growth Hormone. Reviews of metabolic effects appeared.[742, 1512] As might have been anticipated, growth hormone stimulated fibroblastic proliferation and formation of collagen fibrils.[63] More evidence of species specificity appeared.[1745] Its action in vivo was dependent upon a proper balance of adrenocorticoids, thyroxine, and insulin.[742]

Sex Hormones. The rate at which injected liquids or dye solution disappears or "spreads" served as an index of the "barrier" state of the connective tissue; the index was influenced by various hormones, including the sex hormones.[1607] Estrogen caused a reduction in this index in mice,[642] and this effect was not related to the state of tissue hydration.[641] Estradiol increased uptake of labeled glycine in guinea pig symphysis pubis,[1057] and in chickens it impeded cartilage growth.[1495] In the human female, the hormonal changes associated with pregnancy caused proliferation of gingival connective tissue.[1099] Testosterone stimulated the connective tissue in cocks' combs as measured by increased mucopolysaccharides.[3038]

Relaxin. Relaxin, a nonsteroid hormone associated with pregnancy, was found in many different female mammals, including cats, dogs, horses, rabbits, pigs, guinea pigs, and human beings.[2663, 2782] In female animals primed with estrogen, relaxin increased mobility of the symphysis pubis.[684] Proliferation of

capillaries found in the symphysis suggested that depolymerization of the glycoprotein occurred.[2782] Softening of the uterine cervix occurred in pregnant women treated with relaxin, although effects on the symphysis were not definite.[895]

Carrageenin. Carrageenin, a sulfated polygalactose extracted from Irish moss, was useful for experimental stimulation of collagen proliferation. When injected subcutaneously into a guinea pig, carrageenin produced a granuloma which contained a large amount of collagen after 14 days.[3313] The incorporation of S^{35} into the collagen of such a granuloma was studied.[2842]

β-amino Propionitrile. The administration to animals of a sweet pea diet or the lathyrus factor (β-amino propionitrile—BAPN) was reviewed.[2461] The lathyrus diet in rats resulted in proliferation of fibroblasts, lysis of elastic fibers, and increased acid mucopolysaccharides in the ground substance of the aorta.[3345] Hexosamine content of epiphysial cartilage was decreased in lathyrism in the rabbit;[510] BAPN decreased collagen formation in granuloma pouches.[1620, 2135] Similar alterations in healing of turpentine abscesses in the rat after administration of amino acetonitrile[503] and a lathyrus diet[920] were reported, but subperiosteal new bone formation and exostosis developed.[2667, 3381] The bone change was most marked at the site of tendon insertion. Lathyrus-induced skeletal changes were prevented by cortisol,[2730] thyroxine,[2735, 2736] tri-iodothyronine,[2421] and estradiol,[2736] whereas growth hormone promoted skeletal overgrowth.[2731]

Serotonin. Increasing interest in serotonin (5-hydroxytryptamine—5-HT) was due to its role in the response of connective tissue to injury. The results of pertinent research were reviewed.[1882, 2317, 2334] In the rat, the highest concentration of 5-HT was in the outer epidermis.[2345, 2348, 2350] Release of serotonin was accomplished by the administration of reserpine,[2347] and by the production of anaphylaxis.[2344, 3187, 3188] In guinea pigs, rats, and rabbits, administration of 5-HT was followed by increased capillary permeability;[2921] the resulting edema was rich in protein.[2621] Lysergic acid[791] and other antimetabolites[806] inhibited such edema. Sodium salicylate also inhibited the edema-producing effect of 5-HT in the rat,[1657, 1658] and its vascular effects in man.[1157] [Information about the role of serotonin in human physiology and pathology is accumulating. Its importance in the carcinoid syndrome is well known. The relationship of 5-HT to peptic ulceration, psychoses, and hemostasis was described in a recent comprehensive review of serotonin (Sjoerdsma, A.: New England J. Med. **261**: 181, 1959).—Ed.]

Papain. The administration of papain to rabbits resulted in a "softening" of cartilage and in ear collapse,[2048] with a loss of chondroitin sulfate from the disordered cartilage remaining,[3129] and inhibition of longitudinal bone growth.[1500] Depletion of glycogen in liver cells and tubular hemorrhages in the kidneys of rabbits were reported.[2926]

Experimental Arthritis

Bacterial. Naturally occurring infection of mice by *S. moniliformis* was reproduced by subcutaneous, intraperitoneal, intravenous, or intranasal inoculation, and by feeding and contact with rats, although the mouth and throat rather than the gastrointestinal tract were considered to be the natural portals of entry;[1050] agglutinin titers against sensitized sheep cells were significantly higher in rats infected with *S. moniliformis* than in noninfected controls.[2942] A strain of *S. moniliformis* from old laboratory rats given intravenously to young rats produced "acute" osteoarthritis. Histologically, the lesions of arthritis, peri-

arthritis, osteomyelitis, and periostitis became fibrotic and proliferative by the thirty-third day.[1862]

Several methods for experimental production of connective tissue diseases were described.[2737] Polyarthritis in rats, produced by injection of a tumor exudate of Murphy rat lymphosarcoma, was attributed to *Nocardia asteroides* infection;[1563] the adrenal cortex played a "decisive role."[2737] [This was not defined.—Ed.]

Intravenous injection of *Klebsiella pneumoniae,* crude protein and polysaccharide fractions therefrom, and somatic antigens of *Shigella paradysenteriae* produced proliferation of synovial cells and exudate in guinea pigs; antibody was not involved in the synovialis.[1592, 1594, 1596] Polysaccharide complexes of *K. pneumoniae* labeled with C^{14} by biosynthesis rapidly entered joints in the guinea pig; C^{14} remained in the joint space and synovial membrane for several days.[1592] Autoradiographs showed radioactivity to be localized within the synovialis within a few hours, and indicated a direct local effect of this mucopolysaccharide which led to proliferation of synovial cells.[1595]

Serial study of chick embryos inoculated with pleuropneumonia-like organisms revealed hyperemia of articular tissues after five days, necrosis of the synovialis and, after eight days, organization of articular cartilage and fibrous tissue.[2213]

Acute and chronic erysipelas (chronic arthritis in 37%) was produced in swine by six artificial routes of exposure,[2805] and in rabbits given *Erysipelothrix rhusiopathiae* intravenously,[1182] but chronic polyarthritis was produced in only one of five swine intravenously given organisms isolated from an acute septic case.[2805] Serum protein and glycoprotein changes in swine were reported.[2788] Commercially prepared bacterin gave swine partial immunity against swine erysipelas for six weeks, but increased the incidence (62% vs. 14%),[2248] or did not prevent development of chronic polyarthritis.[2806] Penicillin and antiswine erysipelas serum reduced the incidence of chronic arthritis to less than 1%.[2805]

Pathologic similarities to R.A. were described again;[2803, 2807] after one year, changes of osteoarthritis were superimposed upon the "rheumatoid arthritis-like joints."[1182] [We agree that "results of experiments such as these cannot be held to have any direct bearing on the pathogenesis of human arthritis,"[1182] other than those of bacteremic origin.—Ed.]

Sensitizing Agents. A polyarthritis in rats which "simulated" R.A. was produced after intracutaneous, subcutaneous, or intraperitoneal injection of a Freund type of emulsion into which skeletal muscle was incorporated.[2367] [The addition of skeletal muscle was found later to be unnecessary (Pearson, C. M.: Second Pan-American Congress on Rheumatic Diseases, June 5, 1960, Washington, D. C.). —Ed.] The adjuvant, either with or without egg albumin as an antigen, also produced in rabbits a severe chronic inflammatory "anaphylactic arthritis" after three months.[2299] Though similarities to pathology of human rheumatoid arthritis were noted, "the identification of such changes with any human counterpart is unwarranted."[2367] [We agree, but this investigative approach merits further attention.—Ed.]

Dense concentration of C^{14} in synovial membrane and synovial fluid of guinea pigs injected with C^{14}-labeled bacterial polysaccharides suggested that "joint lesions may result from the direct action of foreign mucopolysaccharides within the synovium. . . ."[1593]

An anti-inflammatory fraction isolated from granuloma pouches in rats gave positive color reactions for steroids, and was effective against formalin-induced

arthritis.[2537] Rats injected with exudate of a Murphy rat lymphosarcoma were protected from polyarthritis, with or without adrenalectomy, if homologous exudate was used.[1563] A gold salt (Myochrysine) was effective in preventing the articular lesions in both intact and adrenalectomized animals.[1564]

Carotid-jugular cross-circulation, or a temporary arteriovenous shunt, produced localized, acute necrosis of the heart, arteries, and mitral and aortic valves, cellular reactions, hemorrhage, and fibrinoid lesions in 75 to 100% of 79 rabbits; the mechanism of the reaction was not identified.[736] Also in rabbits, repeated antigenic insults of bovine albumin, bovine gamma globulin, and albumin and globulin together produced marked acute necrotizing arteritis, closely resembling the different morphologic variants of human periarteritis nodosa.[1408]

In dogs given 200 mg. of hydralazine orally at daily intervals for 26 weeks, L.E. cells were found only occasionally, and "seldom resembled the classical L.E. cell." [1103] "The experimental hydralazine syndrome is an entity of much interest [but] its relationship to SLE can not be accepted as proven." [1103] [Thus anticipation that Comens' work, published in 1956, would be confirmed appears to have been dampened.—Ed.]

Hormonal Production and Influence. Cortisone, in doses roughly equivalent to human therapeutic doses (116 to 200 mg. over 29 to 50 days), favored rather than impeded induction of *Erysipelothrix* arthritis in rabbits, but the granulomatous reaction was less florid.[1182] Cortisone, given six weeks after infection was induced, did not affect the course,[1182] but remission of symptoms occurred.[2805] The mineralocorticoid : glucocorticoid ratio might be "concerned in the development of advanced chronic arthritis in swine." [2804]

"Cortisol, ACTH, or thyroxin inhibit, while STH [somatotropic hormone] or partial hepatectomy augment the bone changes" induced by amino-acetonitrile in rats.[2732, 2735, 2738] Cortisol decreased the incidence and severity of arthritis, and partially reversed the polysaccharide-serum protein (PR) ratio of rats given an exudate from Murphy rat lymphosarcoma; phenylbutazone had no consistent effect.[1417]

The injurious (osteoarthritic) effects of anterior hypophysial secretions on the joints were present in underfed animals, and were therefore within limits "at least independent of the amount of food consumed." [2811] [The incidence of osteoarthritis (54%) was still less than that (80%) resulting from effects of pituitary secretions when diet was unrestricted; control values were 25 to 41%, respectively. —Ed.] Diffuse polyarteritis in rats given estrogen and follicle-stimulating hormone was associated with "tumerous changes" in the pituitary and cortical adenomas of the adrenal; mineralocorticoid secretion (aldosterone?) from the latter was considered to be responsible for this vasculitis.[2382]

Nutritional. Necrotizing angiitis and periarteritis of various kinds, produced in rats by 100,000 units of vitamin D per kilogram per day for five days, simulated the arteritis produced in rabbits after massive intravenous doses of horse serum, in rats after drastic interference with renal function, and in man after spontaneous rheumatic or pararheumatic diseases.[1142] A common underlying mechanism, dependent upon derangement of a particular function of the kidney, was postulated. [The doses of vitamin D were obviously large and presumably toxic. Confirmation and elaboration of this study will be awaited with interest.—Ed.] In a strain of mice (C57BL) previously shown to be prone to the development of degenerative joint disease, a diet enriched with 25% lard

both increased the incidence and accelerated the progress of osteoarthritis.[2810] This dietary effect resulted from a primary defect of metabolism or endocrine function.[569]

Trauma. The importance of a film lubricant to the mechanical efficiency of joints was confirmed by reducing the viscosity of synovial fluid of the ankle of dead rabbits and subjecting the joint surfaces to compression and prolonged mechanical exercise.[168] There was "no real healing" of the untreated control knee joint of anesthetized rabbits subjected to a measured degree of trauma and twisting; early intra-articular use of hydrocortisone produced "definite increase in healing."[1036]

Other. A type of vinyl sponge (Ivalon) which stays soft and spongy when wet remained in place in 36 knee joints of 26 dogs, and full motion was regained.[599] Experimental partial and total patellectomy in dogs was followed by degenerative articular changes.[758]

Forty milligrams of phenylbutazone daily for 21 days "aggravate[d] the skeletal changes" produced by amino-acetonitrile given to rats.[2732] A marked increase in rat tissue mast cells in gastric smooth muscle after calciferol and in diaphysial marrow after lathyrism was observed.[1143]

The "formalin-arthritis" technic was used in adult male adrenalectomized rats to show that phenylbutazone in 15 mg. doses orally was as effective antiarthritically as cortisone in 5 mg. doses intramuscularly.[1273] Gold sodium thiomalate (1 mg. four times daily) and sodium salicylate (120 mg. orally) were next in order of effectiveness; 19 other drugs or herbs were tested.

Spontaneous Arthritis in Animals

Further studies of an "important"[2314] arthritic disease of chickens indicated that the causative "agent" differed from "the bacterial type reported previously by various investigators";[666] a small bacterium or large particle virus differentiated from pleuropneumonia-L organisms was suggested.[2316] Effective,[2314, 2778] ineffective,[666, 2314] and noninfluential therapy[2778] was noted. A "hitherto unrecorded" spontaneous myopathy of unknown cause in adult sheep accounted for symptoms generally attributed to scrapie, and "in many ways" resembled dermatomyositis (polymyositis) and muscular dystrophy in man.[346] [There was more "degeneration" than "inflammation," and the grouping together of polymyositis and muscular dystrophy does not coincide with current clinical concepts of these diseases. It is frequently difficult to differentiate between muscular dystrophy and polymyositis, not only clinically but sometimes by muscle biopsy as well. See Section on Myositis.—Ed.] In guinea pigs, a fulminating and apparently spontaneous myositis of uncertain cause could be transmitted by inoculation to other guinea pigs but not to different animals.[2674]

A "new virus" causing arteritis in horses and abortion by mares[792, 793] was the "first viral agent to be identified with selective affinity for blood vessels. . . . A specific microscopic lesion in the media of small muscular arteries" showed "striking similarity to . . . those lesions of periarteritis nodosa in man and cattle."[1597] [Further studies are indicated before definite conclusions can be drawn from this statement.—Ed.]

A syndrome of polyarteritis nodosa, splenomegaly, lymphadenopathy, adrenal enlargement, and hypertrophic osteoarthropathy associated with chronic lympho-

cytic leukemia in rats was capable of serial passage in preweaning rats; cortisone (10 mg. per kilogram for 10 weeks) ameliorated the syndrome.[3248]

Monarthritis or polyarthritis was "the most characteristic symptom of *Streptobacillus* infection" transmitted via the nose and throat from healthy albino rats in an epizoötic in stock strain mice.[1050]

Ery. rhusiopathiae was cultured from 63% of crippled or arthritic joints of swine, but arthritis was found in only 1% of hogs examined in a slaughterhouse.[2622] Pathologic similarities to rheumatic arthritis were reiterated.[2803] Vaccination did not prevent but rather increased the incidence of arthritis.[2248]

Murine osteoarthritis closely simulated the human counterpart in anatomic features, postural distribution, and occurrence in older age groups.[2900, 2901, 2902] Castration of male or female mice delayed and minimized osteoarthritis.[2812, 2813] The lower susceptibility of female mice to osteoarthritis could not be explained by ovarian activity;[2812] genetic factors were important.[2901] The laboratory rat appeared to be resistant to osteoarthritis; preservation of ground substance of soft tissues of the knee of the aging rat coincided with the relative stability of cartilaginous matrix.[2902] Degenerative articular disease in guinea pigs often involved four legs but was not explained by weight-bearing.[2817] Spinal osteoarthritis was "fairly evenly distributed among popular canine breeds," but was most common in dachshunds,[1153] in whom calcified intervertebral thoracic discs were observed.[2434] Cats[1153] and the gorilla[2941, 2942] also were affected by osteoarthritis. Various types of arthritis occurring in small laboratory animals were summarized.[2899]

Suppurative arthritis following trauma in domestic swine, horses, sheep, and cattle, was studied radiographically;[2929] in cattle, extensive bone destruction and extra-osseous new bone formation became evident within two weeks after the initial injury.

Reports of single cases in dogs described spinal tuberculosis (bovine type),[2256] *C. neoformans* infections initially presenting signs of septic arthritis,[1645] and hypertrophic osteoarthropathy with a malignant mixed cell pulmonary tumor[1955] and with metastatic tumors to the lung.[395, 1471] The "first reported case" in the United States of arthritis due to pleuropneumonia-like organisms (not L-form) in a two month old calf "since the eradication of bovine pleuropneumonia" appeared.[2212]

Rehabilitation in Rheumatic Diseases

[The introduction of this section reflects the increasing interest in rehabilitation of patients with rheumatic diseases, as a part of increased interest in rehabilitation of patients with other chronic illnesses. Previous reviews have included references to rehabilitation in the sections on therapy of the particular rheumatic disease.—Ed.]

Definitions. Basic ideas concerning rehabilitation were presented;[525, 1692, 1702, 1950] rehabilitation was defined succinctly as a "concept of humanitarianism,"[204] or as "the process of restoring the handicapped individual to the fullest physical, mental, social, vocational, and economic usefulness of which he is capable."[145, 2635] Rehabilitation was basically the attending physician's responsibility,[639, 2634] but the advantages of a "team approach" using medical and paramedical personnel and services, were stressed.[9, 360, 567, 601, 639, 971, 1139, 1336, 1435, 1438, 1803, 2558]

Objectives. Standardization of rehabilitation for R.A. was difficult "because of the number of variables"[567] incident to the patient and his disease.[639,

[1948, 2558] Functional capacity was related more directly to disability than to disease activity.[1170] The goals of patient and physician needed to be in agreement.[2558] The "most difficult goal" was placement in a suitable occupation.[1950, 2558]

The type of arthritis and extent of joint damage were major factors in rehabilitation.[360, 1950] Of 100 patients, aged 55 to 78 years, attending a rehabilitation center, 79% had degenerative arthritis and 3% had residuals of R.A.[33] Appropriate use of other medical, physical, and surgical therapies was indicated;[217, 567, 677, 1439] "human engineering"[1949] or "tricks . . . to circumnavigate disabilities"[1703] were often required, but the patient's motivation was still the most important factor for success.[9, 638, 639, 1139, 1437, 1948, 1986]

Rehabilitation Services. In the United States there was no institution devoted exclusively to the rehabilitation of arthritic patients. The objectives, functions, plans of organization of rehabilitation centers, and their importance to the total scheme of rehabilitation were the basis of several reports.[1935, 2252, 3117] The development of such centers and services supplemented rather than supplanted "the functions of the practicing physician,"[2634] and had "become characteristic of our age of mass production."[1139]

The greatest hope for extension of rehabilitation services was the use of existing community hospital facilities and health agencies.[1692] A modified hospital annex[1767] and a home-care program for convalescents under hospital direction[2228] were described. Another home-care program was reviewed.[1947] [These were not specifically designed for arthritics.—Ed.] A home-care program for arthritics in a semirural community was initially encouraging.[1985] [This project was only a few months old; no detailed results were given.—Ed.]

The development and acceptance of sheltered workshops not only for the arthritic cripple but also for the more severely handicapped from other causes indicated their effectiveness.[961] More study of sheltered workshops as a channel for rehabilitation of rheumatic patients was urged.[360]

Mobile Physical Therapy Units. A mobile home-therapy unit was practical for severely affected R.A. patients;[1438] in the first year of operation, 23.5% of the cost was recovered in treatment charges, but if the patients had been hospitalized, each would have had treatment charges equivalent to all the costs in 10 days. Use and abuse of mobile physical therapy units in one center in Great Britain were discussed.[142] [The major contribution of such home programs is that they provide these services to large numbers of disabled persons who would not, for various reasons, receive them otherwise.—Ed.]

Results. The first three years' experience with a "back-to-work" program for psysically handicapped arthritics was reported.[9, 1986] Of the group, 58% had R.A., 14% had osteoarthritis, 10% had rheumatoid spondylitis, and 18% had other articular disease. Patients with R.A. returned to work at the same rate as did the group as a whole; even extensive physical impairment did not seem to preclude return to self-support in a competitive labor market.[9] Half of the patients were treated for less than six months, most for less than 12 months;[1986] of 159 patients dismissed in 30 months, 62 had returned to work; 52 did not complete the rehabilitation program, 31 were considered to be unsuitable for the project, and 14 were "referred to other agencies."[9] The results of a most encouraging study were summarized at the end of four and one-half years.[2633] Of 332 arthritic patients trained for competitive jobs, 133 (40%) had gone back to work, and most had continued to work. Of 283 patients age 40 or over, 96

returned to work. This project showed that a "substantial proportion of arthritic patients could be placed in employment after vocational rehabilitation and the majority of those thus placed [could] hold their jobs." [These reports contain additional details and analyses. The types of arthritis, unfortunately, were not specified.—Ed.]

Five-year results of a rehabilitation project on 38 carefully selected patients with R.A. showed that nine of 17 previously severely disabled patients, and 13 of 21 less severely disabled, were still partially or completely self-sufficient; seven were still doing full or part-time work.[1948] Maintenance of physical gains was "directly dependent upon continued control of the disease process."[1948] [A previous report of this pioneer study was abstracted in the Twelfth Rheumatism Review. —Ed.]

Of 24 arthritics who had received in-center treatment for an average of 52 days two years previously, eight were "gainfully employed," and four were either on in-training job programs or at vocational schools; yearly income averaged more than twice their rehabilitation costs.[1382] One patient had osteoarthritis, three had post-traumatic (fracture) arthritis, and 20 (83%) had R.A.; of the last, 11 were independent, six partially dependent, and one was still dependent after the treatment; two had died during the two-year follow-up period.[1382]

Results in "a picked group" also were reported from Vancouver.[1170, 2558] Ninety-five patients had R.A., 22 had rheumatoid spondylitis, five had osteoarthritis, and three had other rheumatic diseases. The average stay in the rehabilitation center was three months. Seventy-one were unemployed before the program, only 47 afterward; most of the latter were still incapable of work. The earnings for two years of 15 of 21 male patients with R.A. and 12 of 13 men with rheumatoid spondylitis rehabilitated to full or part-time work exceeded the costs of their rehabilitation, but this factor was only "a conservative estimate of the impact of the rehabilitation program."[2557] A better work prognosis for the spondylitic was noted.[2557] [The reader is encouraged to consult these papers for more detailed analyses of the results of these projects.—Ed.] Patients were a selected group,[9, 2557, 2558] given intensive placement aid.[1986] A change in attitude of some poorly motivated patients was attributed to the "environment" of the rehabilitation center, but often "our pre-admission assessment of the patient's mental attitude was inadequate."[2558] Adequate follow-up and home-care programs were of "utmost importance" after discharge from a rehabilitation center,[1382] but physical rehabilitation of the disabled patient with R.A. was still "a complex problem."[1948] [The studies so far reported represent sincere attempts to evaluate a difficult but important aspect of the therapy of rheumatoid and other arthritic patients. Though "general results" are usually "encouraging" and the few available specific detailed analyses even more encouraging, there is urgent need for other similar and more extended studies, and especially for more analyses of results and costs according to specific diagnostic criteria, such as those of Robinson[2557] and Heather.[1382]—Ed.]

The Campaign Against Rheumatism

The growing interest in the rheumatic diseases in a wide diversity of scientific disciplines was reflected in the number and quality of papers included in the present Rheumatism Review. There were also an awakening of public interest and an increased awareness of the need for better facilities for patient care, and for more competent teachers and additional research workers.

Scientific Organizations.

La Ligue Internationale contre le Rhumatisme. The Ninth International Congress on Rheumatic Diseases in Toronto, Canada, in June, 1957, was sponsored by La Ligue, with the Canadian Rheumatism Association as the host society. This highly successful meeting was attended by over 1,200 physicians, surgeons, and medical scientists from over 40 countries, and more than 200 papers were read on the diagnosis, treatment, and rehabilitation of persons suffering from rheumatic diseases.[482, 1580] The Swedish Rheumatological Society celebrated the thirtieth anniversary of the founding of the committee which later developed into La Ligue Internationale contre le Rhumatisme at the Sixth Scandinavian Congress of Rheumatology in Lund, Sweden, in August, 1956.[885] [More than 400 medical delegates and 200 associates attended the last meeting of the European Ligue in Istanbul in September, 1959. The Tenth International Congress on Rheumatic Diseases has been planned for Rome, September 4–7, 1961. The third edition of the Year Book of the Ligue, giving a survey of rheumatology, the officers, and a roster of members in each country, is being prepared by the Secretariat (Prof. Agr. F. Delbarre, of Paris) for publication in 1960.—Ed.]

American Rheumatism Association (ARA). The history of the ARA was reviewed from personal knowledge by two active and early participants.[527, 2944] The interesting and comprehensive account by Dr. Robert M. Stecher, who has served as President of both the ARA and La Ligue Internationale contre le Rhumatisme, contains significant documents and memorabilia.[2944] The goals of this professional society were again defined by Dr. Joseph J. Bunim, President (1958–1959): "To expand the boundaries of our clinical and scientific knowledge of the rheumatic diseases and to disseminate this knowledge to our students, colleagues, and associates toward the end of achieving a clearer understanding of the biochemical, genetic, physiologic, and morphologic disorders that produce these diseases and the measures that might ameliorate, correct or overcome them and prevent this progression or hopefully even their appearance."[438] [The twenty-fifth anniversary of the founding of the ARA was celebrated during the Sixth Interim Scientific Session, Detroit, in December, 1959. There were 1,423 members of the ARA in July, 1960; the membership has doubled since 1949.—Ed.]

After several years of deliberate consideration and thoughtful planning, the ARA authorized the publication of a new bimonthly journal, *Arthritis and Rheumatism,* as the official organ of this body. The first volume appeared in February, 1958, under the editorship of William S. Clark, M.D., who qualified for this appointment by his experience in internal medicine, especially in rheumatic diseases, in productive clinical investigation, in academic teaching, and in medical organization. Under the direction of a rotating publications committee elected by the ARA, the new editor and his staff charted a course which would be "flexible in order to meet the changing needs of scientific communication in this particular field of interest. Reports of original investigations relating to the nature, causation, and treatment of the various rheumatic disorders and seemingly pertinent biologic research will be given preference in acceptance of articles for publication."[566]

Another publication of the ARA was the *Primer on Rheumatic Diseases,* which contains basic material concerning rheumatic diseases in a simple and concise form, and is particularly valuable for the general physician and the student. [The fifth edition of this booklet, by a committee of the ARA under the chairmanship

of D. C. Crain, M.D., has recently been published (J. A. M. A. **171**: 1205 (Oct. 31); 1345 (Nov. 7); 1680 (Nov. 21) 1959).—Ed.]

International Society for the Welfare of Cripples. The Seventh World Congress of this Society was held in July, 1957, in London. This meeting provided a forum for the discussion of all aspects of rehabilitation, including rheumatism. The theme of the congress was "Planning for victory over disablement: the advance, integration and application of knowledge."[132]

Foundations and Endowments.

Canadian Arthritis and Rheumatism Society (CARS). Ten years ago this voluntary agency was set up to stimulate a nationwide attack on arthritis. At that time, specialized treatment services for the arthritic sufferer were almost nonexistent; only five hospitals conducted arthritis clinics; there were no mobile physical therapy units, and there was very little arthritis research. In 1958, physical therapy was provided in nearly 200 communities, 50 fellowships were established to provide young physicians with advanced training in rheumatic diseases, and many research projects at university medical schools were financed by grants from CARS and the Department of National Health and Welfare. Contributions to support the Society's activities had increased from $28,737 in 1948 to $951,914 in 1958.[483]

Gairdner Foundation. In 1958 this Canadian foundation announced its first international awards in arthritis and related diseases, totaling $40,000. Prof. H. M. Rose and C. Ragan, M.D., (Columbia University, New York) were among the recipients for their discovery of an agglutinating reaction affording the first practical laboratory blood test for the diagnosis of rheumatoid arthritis.[1092]

Empire Rheumatism Council. In the British Empire this Council, under the chairmanship of Dr. W. S. C. Copeman, financed an extensive program of research, a mobile field survey unit, traveling scholarships, and the multicenter drug evaluation program. The endowment for 10 years of a new chair of rheumatology in the University of London at the Postgraduate Medical School was announced.[867] Prof. E. G. L. Bywaters was named to this high position. [This Council has already endowed a chair at the University of Manchester.—Ed.]

Nuffield Foundation. The total amount devoted to medical research by this Foundation over a 12-year period was £875,000, including £295,000 for rheumatism. In the tenth annual report (1954–55), nearly half of the sum of £106,560 for medical research was for research into rheumatism.[873] The Oliver Bird Building, to house the clinical and laboratory research of the Rheumatic Unit, Northern General Hospital, Edinburgh, under Dr. J. J. R. Duthie, was contributed by this Foundation.

Arthritis and Rheumatism Foundation (ARF). During its tenth anniversary year (1958), this voluntary agency, devoted exclusively to the problems of the rheumatic diseases, raised $3,600,000.[111] Within a 10-year period, the annual contributions received by the ARF increased ninefold. This remarkable progress was due to the continued guidance of its chairman, Mr. Floyd B. Odlum, its president, General George C. Kenney, and the dedicated efforts of the Medical Director, Dr. Russell Cecil. There were 53 chapters in 41 states and the District of Columbia, and several more were under development. [In the year beginning July, 1960, the ARF awarded 41 research fellowship grants totaling $285,000,

and the chapters supported research projects in the amount of $380,000, and raised more than $4,000,000 during the 1959–1960 campaign.—Ed.]

Furnishing a basic educational tool, the ARF, in coöperation with the National Institute of Arthritis and Metabolic Diseases (NIAMD) and the Armed Forces Institute of Pathology, produced a collection of 100 lantern slides which illustrate the pathology of various rheumatic diseases.[1579] [The *Bulletin on Rheumatic Diseases* is prepared and distributed monthly by the ARF. This publication provides a medium for concise and timely articles in both research and clinical areas. The *Bulletin's* circulation has doubled in the last four years and is now 41,000; it is translated into Spanish and Portuguese in the *Archives of Interamerican Rheumatology*. The Second Collection, Volumes V–VIII, 1954–1958, may be purchased from the ARF, 10 Columbus Circle, New York 19, N. Y.—Ed.]

Helen Hay Whitney Foundation. This Foundation was established in 1947 for the express purpose of stimulating and supporting research pertinent to the solution of the problem of rheumatic fever and rheumatic heart disease, but has recently broadened its approach to the problem by including the study of connective tissue and its diseases.[1394] From the beginning of operations in 1947, through June, 1957, support for research had totaled $1,917,600.

The National Foundation. In the summer of 1958 the National Foundation for Infantile Paralysis (Polio), which for more than 20 years had supported extensive research in the field of poliomyelitis, announced that it was broadening its program to include congenital deformities and arthritis. [Upon the initiative of Mr. Floyd B. Odlum, Chairman of ARF, negotiations were entered into with representatives of Polio prior to this announcement to explore the possibility of a combined effort by these voluntary health agencies toward the conquest of rheumatic diseases. However, mutually satisfactory terms for unifying the two organizations could not be found; the former Polio Foundation, renamed "The National Foundation," added to its diversified program certain aspects of the rheumatism problem, such as limited care for children and adolescents with rheumatoid arthritis, scholarships in various ancillary fields, grants for scientific research, and development of academic rheumatism centers. As of January, 1960, the NF had awarded approximately $1,000,000 in grants for research in the field of arthritis, and grants to four university medical centers to aid in the establishment and conduct of exemplary patient care programs.—Ed.]

The National Institute of Arthritis and Metabolic Diseases (NIAMD). This agency of the U. S. Public Health Service supported a broad program of investigation of the metabolic as well as the rheumatic diseases. There are extensive laboratory and clinical facilities at the National Institutes of Health in Bethesda, Maryland. This Institute also supports an extramural program of grants-in-aid for research to universities and other non-Federal institutions; there are also two programs in the training area financed by the extramural NIAMD budget: one, the direct traineeship program, in which the stipend is paid directly to the individual; the other, the graduate training grants program, which is a grant to an institution for use in training in this area.[1750] [The rapid expansion of the research and training grants programs of the NIAMD since its establishment in 1950 has been phenomenal. In this short span of 10 years, the funds provided by Congress for this extramural program have grown to $38,553,000 in 1960. This remarkable rise has exceeded all expectations. The excellence of the programs supported by these funds has been due largely to the system of advisory councils and study sections, composed of the leading teachers, scientists, and physicians in this field, who serve as consultants. The degree of bureaucratic control has been minimal. It is hoped that, in the future, the Government administrators will continue to seek and

to follow the counsel of such carefully selected, voluntary, nongovernmental advisors. —Ed.]

Campaign Against Quacks and "Sure-Cures." No group of ill persons is more often subjected to "sure-cure" remedies than are the sufferers from rheumatism. It was very heartening to review the report of the Research Subcommittee of the Empire Rheumatism Council which had taken this problem seriously and recorded 157 remedies from all over the world.[89] The first point that emerged from the vast majority of statements about these "curative agents" was that the diagnosis of the disorder that had been cured was completely unknown. With very few exceptions, the number of patients cured or not cured with the same treatment was not given. There was a complete absence of any comparable untreated control group with which the treated group could be compared; this was "hardly surprising in view of the large number of papers written on similar lines still appearing in medical journals in some parts of the world." The probability that a natural remission rather than the curative agent had produced the beneficial effect was thought to be high in many if not most instances.

The book entitled *Arthritis and Common Sense,* by Dan Dale Alexander, was at one time at the top of the best-seller list published by the *New York Times Book Review.* The advertising in this book was charged in 1956 by the Federal Trade Commission with "making false, misleading and deceptive statements." [868] [Since then, a decision upholding these charges was obtained, but this book continues to be sold and advertised. The ARF has conducted a vigorous campaign informing the public and the medical profession of this and other misleading advertisements in the field of arthritis and rheumatism.—Ed.]

Announcement

In the preparation of this Thirteenth Rheumatism Review, 4,490 papers were surveyed. The editors wish to thank their colleagues in this country and abroad for sending reprints of their published reports. Space restrictions made it impossible to refer to all of the articles received. It is planned to prepare future Rheumatism Reviews on an annual basis. It would greatly facilitate the Committee's work in collecting all reprints relative to arthritis, rheumatism, and connective tissue and allied diseases if contributors would automatically send to the Editorial Office, 4200 East Ninth Avenue, Denver 20, Colorado, c/o Dr. Charley J. Smyth, two copies of all future English language publications.

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